CORTISONE THERAPY

MAINLY APPLIED TO THE RHEUMATIC DISEASES

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With a Foreword

by

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FOREWORD

SINCE cortisone was introduced for the treatment of rheumatoid arthritis nearly a decade ago, a vast literature has accumulated about

may be judged by the fact that by some cortisone is regarded as the "elixir vitae", by others as simply a "glorified aspirin". Controlled clinical trials in this country have done much to restore the balance between unbridled enthusiasm and therapeutic nihilism, and the time is now ripe for a reasoned appraisal of the place of cortisone and the newer steroid derivatives in treatment.

Few could be better qualified for this task than Dr. John Glyn who has had the advantage of working during the past few years with some of our most distinguished rheumatologists, and has himself taken part in the clinical trials of cortisone in this country and in America. From his personal experience and wide reading he provides in this monograph a comprehensive and judicial survey of the salient features of the

practical
He deals
sorders as
dermato-
well be that cortisone

Not all will approve unreservedly of all the opinions he expresses, and he recognizes that for the solution of many problems on which he gives his present tentative conclusions, further evidence is needed. But this book provides a veritable treasure-house not only for those workers with a dominant interest in this field, but also for those general practitioners, and physicians whose special interests lie outside rheumatology and allergy I warmly commend it

September, 1957 COHEN OF BIRKENHEAD

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TO MY WIFE

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ACKNOWLEDGEMENTS

SEVERAL chapters in this book have been adapted from a thesis submitted for the degree of Doctor of Medicine in the University of Cambridge, and I am grateful to the late Sir Lionel Whitby for permission to use this material.

I am very greatly indebted for the help, co-operation and advice I have received from numerous colleagues and chiefs in all the departments with which I have been associated. I would mention specifically Dr. W. S. C Copeman, Dr. O. Savage and Dr. W. S Tegner, because it was their guidance and enthusiasm which stimulated and then perpetuated my interest in the rheumatic diseases and in cortisone in particular.

I wish to express my gratitude to Dr. P. M. F Bishop, who gave me invaluable help and encouragement in the construction of the original thesis, to Miss E Gask, who performed the difficult task of creating order out of chaos by her secretarial assistance, and, finally, my most grateful thanks to Dr. A. Paton for much editorial advice. To my publishers I owe a special debt for their patience and forbearance.

J.G.

INTRODUCTION

in the history of medicine. During this period the pendulum of world opinion has swung from one extreme to the other, and the value of the

The major part of the book is concerned with the steroid treatment of

diseases since the early days. Another important consideration is that rheumatoid arthritis can serve as the typical example of a chronic disease, in which many of the problems of cortisone therapy may be expected to arise

by an account of their pharmacological properties. A clear understanding of these is a necessary prerequisite to the

schedules of dosage, precautions to be taken and methods of overcoming most of the problems that are likely to be met. The indications for intra-articular injections are outlined in Chapter 5, and this is supplemented by an appendix showing anatomical approaches to the various joints. A comprehensive review of other conditions in which the drugs have been used is contained in Chapter 6. The final chapter

CHAPTER I

HISTORICAL REVIEW

and irreversibly from its time of onset. Indeed a classical description of the disease in 1890 described it as "... one of the most intractable, obstinate and crippling diseases that can befall a human body". Others talked about the "great and lasting feebleness" which the

teristic of the natural history of the disease, their account was purely descriptive, and there was no hint that they were thinking in terms of therapeutic potentialities

There followed the inevitable systematic search for "Nature's dramatic Antidote", in which every conceivable constituent of bile was administered to groups of patients. Other sufferers even submitted to blood transfusions from jaundiced patients and a few were given hepatotoxic drugs in an effort to induce jaundice

attempts to sum up the impact of cortisone on rheumatological practice and research and touches on some of the controversial issues raised by its discovery. Because much of the controversy has arisen from the imperfect nature of our methods for evaluating new treatments in the rheumatic diseases, this problem has received particular attention, and some examples of recommended procedures are included in the appendix. Recent developments and prospects for the future are discussed throughout the book.

Faced with the formidable task of abbreviating a mass of material into a small textbook, it is inevitable that there should be some degree of dogmatism, and that many dissenting opinions have had to be omitted. To the extent that such omissions reflect personal bias, I must bear full responsibility, recognising that it would be impossible to study a drug continuously for eight years without developing certain prejudices. Where however I am conscious of expressing unorthodox views I have tried to make this clear in the text.

17-hydroxy-11-dehydro-corticosterone (" Compound E " or Cortisone) when it became available. The rationale, in retrospect, seems a little

ætiological factor; but when he came to make post-mortem examina-

had chemically characterized these substances in 1937–38. Almost simultaneously they were isolated by Reichstein and by Wintersteiner

quantities in which they were available did not permit clinical experiments until considerably later.

effect of 17-hydroxy-11-dehydro-corticosterone as soon as it became available, which was not for another seven years.

In 1944 the Mayo Foundation produced small amounts of dehydro-corticosterone (Compound A) In 1945 this was produced in quantity

developments emerged both from the Mayo Foundation and from Merck's.

By May 1948, the material was starting to become available in small but increasing amounts. Since then there have been immense and unpredictable improvements in production and, although a *total* synthesis is not yet practicable commercially, the basic limiting factor,

climax For reasons that are still not clear, the investigators chose to use dosages of 100 mg /day. In 1948 this could have been considered a vastly excessive dose in relation to hormone requirements in other conditions Had they used a smaller dose we now know there would probably not have been any result, and the discovery of cortisone might have been delayed for many years.

Secondly, the size of the crystals in their preparation happened to

It was again Hench and his co-workers at the Mayo Foundation who first began to appreciate the relative constancy with which patients improved during their pregnancy, only to relapse, in the majority of cases, in the puerperium.

The conviction grew that the remissions in jaundice were analagous to those in pregnancy, and indeed that they were probably due to the same agent Hench started to explain these phenomena in terms of a hypothetical " Anti-rheumatic substance *X* " and stated that ". . . if the

metabolites whose concentration in the blood was known to increase in pregnancy and jaundice. As early as 1939 one finds references to cholesterol, ergosterol, sex hormones, bile acids and even Cortin (whole adrenal extract) in this connexion, but gradually the emphasis came to

known sex hormones, the responsible hormone must inevitably be common to both sexes.

Similarly the exclusiveness of pregnancy and jaundice as agents

be irreversible, and the physiological ravages which he regarded as potentially reversible In illustration of this idea he evoked the meta-

have been very carefully "screened" before selection, and patients who—within the limitation of our knowledge—were likely to develop serious side-effects were eliminated.

Secondly, the drug was given with extremely careful clinical and laboratory control, so that side-effects could be detected and dealt with in their earliest phases.

By contrast, in the United States, as soon as supplies became available, they were distributed through ordinary commercial channels so that economic and personal factors frequently took precedence over purely clinical ones in case selection.

Furthermore, much of it was administered by clinicians who had not had the opportunity of gaining experience either in the rheumatic diseases or in the special problems which are implicit in hormone therapy. These factors combined with dosage regimes which we now know have been grossly excessive were responsible for an appalling legacy of side effects in some parts of the United States.

[illegible]

3. The Search for Analogues and the Discovery of the Specificity of Cortisone. The discovery of any new drug is generally followed by a search for simpler, cheaper, safer or more effective analogues. In the [illegible]

Reversibility" was valid.

(*b*) It was stated categorically by experienced chemists that it would never be possible to produce a fraction of the quantity necessary to meet clinical requirements, and that as a result the practical application of the discovery would always be limited by economic and technical factors.

(*c*) Cosmetic and other serious side-effects were caused by cortisone.

(*d*) There was complete ignorance of the vital pharmacological action of cortisone. This enabled workers to take an extremely catholic [illegible]

acted therapeutically

It took a long time before the remarkable specificity of cortisone and hydrocortisone was appreciated

[illegible]

be absorbed at approximately the right speed. Had they been larger, absorption would have been slower and the clinical remissions far less dramatic.

In August 1948 a patient with rheumatoid arthritis in the Mayo Foundation failed to get jaundice or relief following lactophenin administration. In September 1948 a letter was written to the Merck Company requesting enough 17-hydroxy-11-dehydro-corticosterone to treat this one patient. On 21st September, 1948, the first injection of cortisone crystals was given to this patient with the dramatic results which are well known. The remainder of this book is, in effect, an ac*count of the results of this injection.*

September 1948—Present Day

The discovery of the clinical potentialities of cortisone precipitated [illegible] year as [illegible] nient to review the progress chronologically. It will therefore be considered under the following headings:

[illegible] reports which appeared elsewhere, not only in medical journals, but also *in the lay press.*

It provides an interesting commentary on the interrelationship of economic and scientific factors in this type of research. Hench's original intention was to carry out an intensive study of the drug's clinical [illegible] his discovery in 1950, or even 1951. [illegible] he quantities neces- [illegible] hat the commercial firm involved was forced to demand corroborative evidence from independent investigators before setting up the machinery for production. [illegible] thus divided up, it did not take the lay [illegible] ce all manner of sensational [illegible] *The early and unbalanced* enthusiasm thus engendered was undoubtedly responsible for the subsequent vicissitudes in the reputation of the drug.

2. The Supply Position. The limitations imposed by the problems of [illegible] in the early days—and of distribution outside the "Hard [illegible] l bearing on [illegible] Atlantic [illegible] untries) had [illegible] this reason [illegible] h purposes. [illegible] d and it did [illegible] December, 1955.

Two important results have stemmed from this Firstly, our cases

the doses in which it was advocated. It is no longer used in practice

Para-amino-benzoic acid is still recommended by at least one group of workers in the United States, but we have been quite unable to

medicine every day before they take their cortisone

Another attempt on the problem was made in the early days by invoking a pituitary "feed-back" mechanism It was hoped that by administering œstrogens simultaneously with the cortisone, the output of some of the other "trophic" hormones of the anterior pituitary would be diminished, thereby decreasing the endocrine side-effects. There is no evidence that this occurred in practice, and the method has been abandoned. Large doses of thyroid have been given on the same principle, and with the same disappointing results.

5 **The Development of Prophylactic Measures.** Perhaps the most

daily administration of 3–4 g. of a potassium salt such as potassium nitrate or chloride

Similarly, the routine administration of testosterone will reverse to some extent the catabolic effect which cortisone has on the body nitrogen and calcium This, however, is expensive, and the complementary virilizing effects of the two drugs make it impractical to use in most female patients.

efforts were usually directed at modification of the steroid nucleus itself, and in a recent book Hench lists more than fifty variants, all of which have now passed into the limbo of obscurity.

It is notable, however, that most of them were originally thrust into prominence by the premature and exaggerated claims of enthusiastic workers who did not appreciate that the natural history of rheumatoid arthritis is to show cyclical variations in activity. This would not have been so serious were it not for the fact that each claim necessitated at least one, and usually several, laboriously planned clinical trials before it could be refuted.

Apart from the waste of time and money thus entailed, there were humanitarian factors to be considered, since most of these steroids were dissolved, for technical reasons, in ethyl oleate, and this appears to be a highly irritant oil, causing severe local tenderness in all cases and large abscesses in those who were less fortunate.

Apart from steroid analogues, there were very many attempts to stimulate

corticotro

liquorice (

None of these claims has withstood the tests of time, but they remain of considerable historical interest.

smaller and therefore less toxic dose.

These efforts have taken one of three main forms: in the first, cortisone has been combined with another, recognized analgesic or "anti-rheumatic" drug, in the hopes that the therapeutic effects will be additive whilst their side-effects will not. To this end, cortisone has been combined with salicylates, with gold, and more recently with phenylbutazone.

Whilst in individual cases these combinations have proved useful in reducing the dose of cortisone below the toxicity level, it is a potentially dangerous approach. This is especially so in the case of

cortisone suppression is removed Furthermore, at least one observer has produced evidence to show that gold and cortisone are mutually antagonistic substances.

dardize the drug in terms of its capacity to deplete the suprarenal cortex of ascorbic acid

The crude methods of extraction employed in the early days frequently resulted in contamination with other anterior pituitary hormones which were responsible for their own side-effects. For example, generalized pigmentation was quite a common occurrence, and women patients found this cosmetically most distasteful. It presumably occurred because of contamination with the melanophore stimulating hormone which is secreted by the anterior pituitary. Similarly contamination with growth hormone produced its own complications including a profound upset of the carbohydrate metabolism. Other complications were allergic in nature and were due to injections of the crude foreign protein material

maximal" stimuli. As a result the technique of continuous intravenous infusions was developed, and it was found that one unit of corticotrophin given in this way was equivalent to about five when given four times a day, and to seven or eight when compared to two injections a day.

refinements.

The third problem, that of producing a long-acting preparation of the hormone, did seem for two or three years to present insoluble problems to the manufacturers, and all of the earlier products were either impossible to inject, intolerably painful to the patient, or had lost most of their biological activity in the course of preparation.

In the past two years, however, there have been several extremely satisfactory preparations on the market, many of which seem to act

which they prove that certain modifications of the diet can substantially reduce the urinary 17-ketosteroid output from a given dose of cortisone, with a corresponding reduction in the unwanted side-effects. The details of their diet would not be easy to carry out in practice without the aid of a special dietetic department. However, in principle it represents the type of diet at which cortisone intolerant patients should aim. (See Chap. 4).

6. **Methods of Administration.** Several other fundamental changes have occurred in the course of the past seven years, for example, the discovery that cortisone, far from being destroyed by gastric and intestinal digestion, is absorbed with its action unimpaired. In fact it was found to be absorbed more rapidly and regularly than the intramuscular injections used hitherto.

In the early days following this discovery it was customary to ask patients to swallow the micro-crystalline suspension as prepared for injection, but the excessively bitter taste was impossible to mask with the customary flavouring agents and the patients found it well-nigh intolerable. However within a very few months the manufacturers had succeeded in preparing tablets, and it is in this simple form that it is now prescribed.

No long-term treatment is pleasant when it means daily injections of a fairly bulky preparation, but the micro-crystalline steroids seemed to suffer from two additional hazards of their own—namely their slow-

but were extremely obstinate in their response to the usual treatments.

7. ***Dosage Regimes.*** Another important change has been in our conception of dosage. This will be discussed in detail later and it is

Many different dosage schedules are reviewed by Hench in one of his latest publications Most of them are now obsolete, but he does stress repeatedly that the dosage schedule must be " tailored " to fit the requirements of the individual patient, and this refers not only to the total amount of the drug he takes in the course of a day, but also how he divides up the dosage in relation to his symptoms, *which are usually* cyclical

The other great mistake which was not appreciated for two or three years was to vary the dose excessively from day to day. We now know that the tissues seem to adjust themselves to various blood levels of circulating hormones, and sudden diminutions of these levels can cause a feeling of profound illness

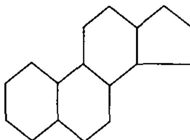
8. **Refinements in the preparation of Corticotrophin.** In the early days

CHAPTER 2

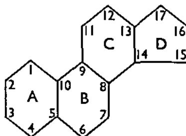
THE NATURE OF CORTISONE AND OTHER STEROID DRUGS

BY 1948, biochemists had isolated approximately twenty-eight discrete steroid substances from the suprarenal cortex, leaving unidentified a large amorphous fraction.

The term " steroid " is a generic one for certain compounds which contain the perhydrocyclopenteno-phenanthrene ring system whose basic chemical structure can be represented thus:



The conventional labelling of the rings and carbon atoms is shown here.



The naturally occurring steroids of the suprarenal cortex can be broadly divided into three groups. The first consists of well-recognized sex hormones The second groups are derived from the amorphous

throughout the twenty-four hours. Indeed many patients can continue satisfactorily with injections on alternate days ... cases need only ...
to inject
intermit

9. **Local Therapy.** Another major advance was the appreciation that hydrocortisone—and to a far lesser extent, cortisone—are active when injected locally. The implications and results of this discovery will be discussed at length in a separate chapter.

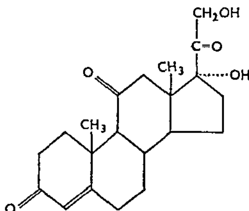
10. **More Potent Steroids.** In 1954 two new compounds, prednisone and prednisolone, were synthesized, which proved ... potent as ...

since May 1950." Althou...
rheumatoid arthritis, they
habit of producing peptic ...

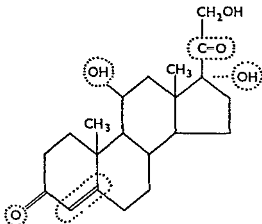
The experience gained in synthesizing new steroids is bearing fruit in another direction. Chemists are ...
grounds what ar
steroid nucleus.
the premise that
is proportional t
true as newer
that laborator
It should soon ... only to screen new compounds in the laboratory before subjecting them to extensive clinical trials (the only means at our disposal up to now), but also to produce the ideal steroid for the particular job in hand.

The remainder of this book is devoted to a detailed discussion of some of the problems encountered in this chapter.

(2) Cortisone (Compound E) is.



(3) Hydrocortisone (Cortisol or Compound F) by contrast is:



The essential parts of this nucleus are circled thus ○.

Mason and Polley, by a process of elimination, concluded that the anti-rheumatic effect of steroid drugs depended on the following characteristics

(1) A ketone group at Carbon-3,
(2)
(3)
(4)
(5)

It will be seen that the *only* difference between corticosterone and hydrocortisone is the hydroxyl group on the " 17 " position, present in the latter but absent in Compound B.

residue which remains after extractions of all the known compounds. Some of these appear to be metabolically inert, but others—such as aldosterone—have now been characterized, and are known to have [illegible] p, which are also [illegible] d by Selye into [illegible] minant effect on [illegible], i.e., those which act predominantly on the sodium and potassium metabolism.

All the steroids which have an "anti-inflammatory" action belong to the "glucocorticoid" group, and they are characterized chemically by a hydroxyl or a ketone radical at the "11" position of the nucleus, and by a hydroxyl group at the "17" position. It is these essential radicals which have caused the major manufacturing problems in large-scale synthesis.

Originally the only starting material which could be used in the commercial production of cortisone was ox bile. The yields were extremely small, and by no stretch of imagination could they ever have been sufficient to provide the quantities necessary even for research, let alone for clinical use.

The Mexican yam was next investigated as a potential source of supply, and at least one of the pharmaceutical companies is now using hecogenin, obtained from the East African sisal plant, which can be grown in profusion. This, coupled with secret technical advances in extraction and synthesis, has largely overcome the supply and cost problems which in the early days seemed hopelessly insoluble.

We shall be discussing the following compounds in the remainder of this book. (See also Tables I & II)

(1) Corticosterone (Compound B) which has this formula:

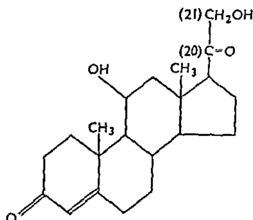


TABLE II

Preparation Available	Mode of Administration
ACTH	
1. Water soluble	Intramuscularly, 4-hourly
2. Incorporated in a zinc menstruum } long acting	Intramuscularly, daily
3. In combination with zinc } long acting	
CORTISONE	
1 25 mg tablets	By mouth
2 Microcrystalline suspension 25 mg/cc	By mouth (suitably flavoured)
3. Long acting microcrystalline suspension (not available yet commercially)	Oily injection—by injection once every 2–3 weeks
4 Eye drops 1%	
5 Ointment 1%	
HYDROCORTISONE	
(a) *Free alcohol*	
1 20 and 10 mg tablets	By mouth
2 50 and 100 mg solutions	Intravenous infusion in saline
3 Ointments 1%, 2½%	Inunction
4 Skin lotion 1%	Spray
(b) *Acetate*	
1 Microcrystalline suspension 25 mg/cc.	Local and intra-articular injections
2 Skin ointment 1%, 2½%	Inunction
3. Eyedrops 1%	Local instillation
4 Eye ointment 2½%	Local inunction
(c) *Tertiary Butyl Acetate*	
1 Microcrystalline suspension 25 mg/cc	Local and intra-articular injections
(d) *Hemisuccinate*	
1 100 mg solution in 2 cc	Intravenous or intramuscular injection
DELTA CORTISONE	
1 1 and 5 mg tablets	By mouth
DELTA HYDROCORTISONE	
1. Microcrystalline suspension (not yet available commercially in this country)	Local and intra-articular injections

These substances are usually prepared in the form of the acetate, although certain other esters are known to be just as active. They consist of white odourless crystals which are relatively insoluble in water and physiological solutions, so that before they were manufactured in tablet form they used to be prepared in the form of microcrystals in aqueous suspension. Such a solution is stable at room temperature

Two of the latest recruits to the therapeutic field are known respectively as delta-cortisone and delta-hydrocortisone. Their most popular trade names are Prednisone and Prednisolone.*

* Originally known as Metacortandracin and Metacortandralone

It is therefore fascinating to learn from Robinson and [illegible]

city may be a good augury for the future, since it is by no means impossible that exactly the reverse can occur, i.e., the production of a steroid which causes maximal therapeutic effect with minimal undesirable reactions.

Hydrocortisone appears to be the natural hormone of the adrenal cortex. Cortisone, which only differs from it by having a ketone rather than a hydroxyl radical on the " 11 " position, is probably not secreted by the human adrenal cortex. The fact that it was the first, and is still by far the most widely used steroid, is largely because it is significantly easier and cheaper to manufacture than hydrocortisone.

TABLE I

Approved Name	Chemical Formula	Abbreviations and Alternative Titles	Proprietary Names
Corticotrophin .	Unknown	ACTH Corticotrophin Adrenocorticotrophic hormone Adrenocorticotrophin	ACTH-ACTH gel (long acting) Cortrophin Cortrophin z (long-acting) Cortico-depot (long-acting)
Cortisone	17-Hydroxy-11-Dehydro-Corticosterone	Compound E	Cortisyl Cortelan Cortistab
Hydrocortisone	17-Hydroxy-Corticosterone	Compound F Hydrocortone Cortisol, H C A.	Cortef Cortril Efcortelan Hydrocortone Hydrocortistab Hydrocortysil
Delta cortisone	Δ_1 dehydro-cortisone	Prednisone Metacortandracin	Decortisyl Deltalone
Delta hydro-cortisone	Δ_1 dehydro-hydrocortisone	Prednisolone Metacortandralone	Precortisyl Delta cortef Delta stab Delta cortril Hydrodeltalone
Hydrocortisone Tertiary Butyl Acetate		Cortisol Tertiary Butyl Acetate	Hydrocortisone T.B A
Fluoro-hydrocortisone	9 alpha fluoro hydrocortisone		
Hydrocortisone Hemisuccinate			

determined until very recently. It has a molecular weight of about 20,000 and is purified by a process of ultra-filtration and concentrated by absorption with oxycellulose.

Several groups of chemists have attempted to hydrolyse this complex molecule to see if the resulting polypeptides retained their physiological activity; and finally the 1955 Nobel Prize was awarded to Li whose [illegible]

[illegible]

only in the replacement of one serine unit by leucine together with a [illegible]

[illegible]

ever, at the moment, it seems that it will be a formidable project.

Corticotrophin has no inherent actions of its own, but depends entirely on the response of the adrenal glands, and whereas it stimulates the cortex to produce a mixture of all its hormones, the only ones which are important in practice are hydrocortisone and the other "glucocorticoids". In fact the therapeutic effects and side reactions of corticotrophin appear to be almost identical with those produced by cortisone or hydrocortisone.

Corticotrophin causes temporary suprarenal hypertrophy and anterior pituitary atrophy. By contrast cortisone and hydrocortisone cause pronounced but reversible atrophy of both these glands.

Other Steroids

[illegible]

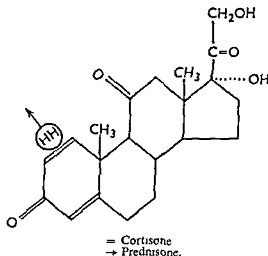
with a salt-retaining hormone present in human urine It is closely related to corticosterone, having an aldehyde instead of a methyl group at the "18" position. In theory the addition of a hydroxyl group at the "17" position should convert aldosterone into a powerful anti-inflammatory agent

[illegible]

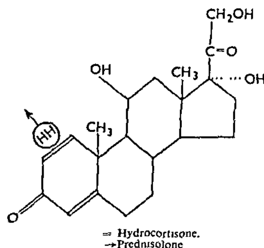
sodium.

The clinical aspects of these substances will be discussed in a later chapter, but it is interesting to note at this stage how such a small change

a double bond for 2 hydrogen atoms in the 1–2 position:



= Cortisone
→ Prednisone.



= Hydrocortisone.
→ Prednisolone

Corticotrophin—ACTH (Adrenocorticotrophic hormone)

This is a hormone of the anterior pituitary. It is a complex protein substance whose molecular configuration remained completely un-

which produce an adrenocorticotrophic hormone (ACTH, corticotrophin). ACTH administration leads to hypertrophy of the cortex, acceleration of the rate of secretion and depletion of the amount of cholesterol and ascorbic acid, which are thought to be precursors of the steroid hormones. Prolonged administration of cortisone causes atrophy of the adrenals.

Adrenal steroids have been divided into two main groups depending on their predominant metabolic action: "glucocorticoids", which have an effect on carbohydrate metabolism, and "mineralocorticoids", which mainly affect electrolytes. While those with glucocorticoid activity are under the control of the anterior pituitary, there is as yet no evidence that mineralocorticoids such as desoxycorticosterone and aldosterone are similarly influenced by this gland.

Any condition which increases the metabolic demand of the tissues causes secretion of hormones by the adrenal cortex, which itself is activated by the anterior pituitary Such conditions have been collected together under the term "stress", since the body responds to all of them in a stereotyped manner. It is not known how the pituitary-adrenal axis is activated by stress, but there are a number of theories·

(*a*) Adrenaline. C. N. H. Long postulated that adrenaline released

steroid hormones which takes place in a matter of seconds if a stress is applied to an animal.

(*b*) Reduction of circulating corticoids. Sayers has shown that there is a reciprocal relationship between the level of ACTH and that of circulating steroids He assumed that stress caused a fall in steroids with a consequent rise in output of ACTH by a feedback mechanism However it has never been shown that there is increased utilization of

s and others
secretion of
the normal
response to stress It is believed that stress stimulates the hypothalamus to release a "neurohumor" which passes via the portal vessels to the pituitary, although so far the nature of this substance is unknown. In addition some people have found that the anterior pituitary can react normally if transplanted away from the hypothalamus

(*d*) Posterior pituitary. There have been some recent claims that the anterior pituitary is stimulated to secrete ACTH by pitressin, but this may be merely an example of a response to stress

(*e*) Electrolyte changes The isolated adrenal gland can be stimulated to secrete in response to changes in local electrolyte concentration. This is probably important in the case of the mineralocorticoids, but it is difficult to see how it could influence glucocorticoids

Selye has produced an elaborate hypothesis, based on the reaction to stress, to explain not only the endocrine response but also the occurrence of certain stress diseases, or "diseases of adaptation" These

CHAPTER 3

PHARMACOLOGICAL PROPERTIES AND SIDE EFFECTS

"In cortisone therapy all we do is to exchange one pathological state for another"—RAGAN

"We have learned no longer to fear the side-effects of cortisone but instead we treat them with respect"—HENCH.

"The preoccupation of many observers with these mild side-effects reminds one of a house-proud woman overconscious of a speck of dust which the visitor has not noticed!"—BISHOP.

SINCE steroids are related to, and in some cases identical with, naturally occurring substances in the body, it is obvious that their proper use depends on a clear understanding of their physiological properties. Since however in many of the experiments on which this knowledge is based large amounts of steroids were used, we prefer to talk about the pharmacological actions. These will be discussed first under the following headings.

(*a*) Pituitary-adrenal axis
(*b*) Electrolyte metabolism
(*c*) Carbohydrate metabolism
(*d*) Fat metabolism
(*e*) Protein metabolism
(*f*) Mesenchymal tissues

A detailed account, arranged by systems, will follow of the side-effects of steroid therapy, and finally some discussion of cortisone addiction and resistance.

PHARMACOLOGICAL PROPERTIES

Pituitary-Adrenal Axis

The adrenal cortex secretes corticosterone, hydrocortisone (cortisol) and probably other steroids in various combinations depending on the species Cortisone is not a natural secretory product.

The adrenal cortex consists of three zones—an outer zona glomerulosa, middle zona fasciculata and an inner zona reticularis It is not know [illegible] for the secretion of a particular [illegible] takes part in [illegible] hormones.

Secretion is under the control of the anterior pituitary basophil cells

of people. Acetylcholine synthesis may also be accelerated, and a reduction in the convulsive threshold of the brain has been reported in animals.

Carbohydrate Metabolism

Equal in importance to its effects on electrolytes, is the action of the adrenal cortex on carbohydrate metabolism. The adrenalectomized animal has a low blood sugar level and inadequate stores of glycogen, so that it is unable to meet the demands of any metabolic stress such as fasting. For this and other reasons it is extremely sensitive to insulin Adrenal cortical extracts restore carbohydrate metabolism to normal in such an animal, and it is hardly surprising that excess steroids in the normal organism can cause hyperglycæmia and resistance to insulin. These effects are brought about chiefly by increased gluconeogenesis, [illegible]

unsettled.

It is not known at what point in the metabolism of carbohydrates steroid hormones exert their action They may possibly inhibit the enzyme hexokinase which is concerned in the phosphorylation of glucose and is said to be acted upon by insulin The finding of diminished glutathione levels in the blood of animals receiving cortisone has led to the theory that there is a failure of synthesis of sulphur- [illegible]

Steroid diabetes is associated with an impaired glucose tolerance test, glycosuria—part of which may be due to a lowered renal threshold—very mild ketonuria and insulin resistance. It is usually temporary, though permanent diabetes has been reported in animals and man after stopping the steroids

Fat Metabolism

[illegible]

fat

The increase in blood cholesterol may however be explained by another mechanism A lowering of the BMR and diminished uptake of radioiodine have been reported in patients on cortisone, thus suggesting some depression of thyroid function.

he believes are due to inappropriate responses on the part of the body to any non-specific stress. He has termed the response to stress the "general adaptation syndrome" in which he recognises three stages.

produced experimental evidence that the mineralocorticoids are inflammatory in nature, producing changes in blood vessels and synovia, similar to those found in stress diseases such as rheumatoid arthritis,

beneficial.

Electrolyte Metabolism

Cortisone, and prednisone to an even greater extent, have a weaker effect on electrolytes than the so-called mineralo-corticoids, corticosterone, desoxycorticosterone and aldosterone. Nevertheless sodium and chloride retention do occur, at least in the initial stages of treatment and may prove troublesome with prolonged therapy. Sodium retention is a general phenomenon, and is reflected in a reduction in the sodium content of urine, sweat and fæces. A direct effect of steroids on the renal tubules has been postulated, and since water is also reabsorbed, a shift of fluid occurs from the cells to the extracellular fluid, *so that the blood volume increases. These effects on salt and water* probably explain the rise in blood pressure, the "moon facies" and the œdema that may result from giving cortisone

Hypertension however has been attributed to other mechanisms, for example, to a direct effect of cortisone on the heart, thus increasing stroke volume, to an increase in peripheral resistance or to the production of pressor substances

At the same time as the sodium retention there is a loss of potassium from the tissues and increased excretion in the urine. This can be explained partly by protein breakdown and partly by a direct action on the renal tubules Weakness, hypotension and a metabolic alkalosis may be produced. A negative calcium balance results from steroid administration.

Cortisone is said to increase the acid and pepsin (as measured by

responsible

(ix) Opposition to the action of the spreading factor, hyaluronidase.

(x) Depression of allergic and hypersensitivity phenomena, for example tuberculin sensitivity.

(xi) Increased sensitivity to drugs, anæsthetics and blood loss

(xii) Depression of mitotic activity. The suppression of nucleo-protein synthesis that occurs may account for the increased uric acid and nitrogen excretion and for gluconeogenesis.

(xiii) Depression of eosinophils, which has had important practical use as a test of adrenal cortical function

(xiv) Variable effects on blood vessels and clotting mechanisms. Decreased permeability, and with sudden fluctuations in dosage a tendency to inflammatory reaction in the vessel wall. Intravascular clotting. Increased prothrombin activity, with an increase in the requirement of anticoagulants On the other hand, fall in fibrinogen levels and release of a heparin-like substance with an increased tendency to bleeding

SIDE EFFECTS

The success or failure of any therapy depends in the long run on the balance between relief of symptoms and dangers of toxicity. With a drug like cortisone the gap between the therapeutic dose and that which causes side-effects (the so-called toxic. therapeutic ratio) may be so narrow as to be virtually non-existent Many uncritical opinions have been expressed on the dangers of the steroids and it is important in a review such as this to steer a middle course

Before entering on a detailed discussion of side-effects however

ever, it should be possible to predict with some degree of accuracy the relative predispositions to toxicity. Thus in general:

and

(v) obese patients tend to be intolerant

Protein Metabolism

Cortisone in large doses promotes the breakdown of proteins (catabolism) and prevents their synthesis (anti-anabolism). To some extent this is offset by an increase in appetite, and may in any case be only temporary, but there is nevertheless a negative nitrogen balance initially. In addition to increased nitrogen excretion, there is a loss of creatinine, uric acid and amino-acids in the urine. The pattern of amino-acid excretion may be altered, for example sulphur is excreted in excess, due to the breakdown of sulphur-containing amino-acids. Liver amino-acid oxidase is stimulated. Failure to build up protein from amino-acids has been shown by experiments in which glycine labelled with radioactive nitrogen has been fed to animals receiving cortisone. The isotope was not incorporated in the tissues at all.

Protein is mobilized chiefly from labile carcass protein of muscles and bone. The mobilized protein is not necessarily lost from the body, and may in fact be distributed in sites where it is urgently needed. Examples of this are the fœtus during pregnancy, healing of wounds and chronic inflammatory processes However this is probably physiological rather [illegible]
ment. [illegible]
point [illegible]

Mesenchymal Tissues

The action of cortisone on the synthesis of protein suggests that it will have widespread effects on all tissues of the body. Perhaps the most important from our point of view, since we are considering inflammation, are the mesenchymal tissues This term embraces con- [illegible]

(i) *Depression of all the elements of the local inflammatory response*

(ii) Depression of the phagocytic activity of the reticulo-endothelial system

(iii) Depression of polymorphs, which do not accumulate at the site of inflammation

(iv) Delayed healing of wounds and fractures

(v) Depression of lymphocytes, and atrophy of lymph glands and spleen

(vi) Depression of antibody production and globulin formation

(vii) Enhancement of all common bacterial, virus, fungal and protozoal infections.

(viii) Decrease in permeability of serous membranes, vessels and cells.

"fluid retention" and "glycosuria" were regarded inevitably as

The effect of personal prejudices in interpretations of these criteria became very evident if an analysis was made of the results recorded by each centre separately. It was difficult to avoid the conclusion that the recorded incidence bore a strong relation to the prevailing views of the centre from which it emanated, a frequent problem in such co-operative trials

Tables I and II are adapted from a recent publication by Hench and illustrate these points well.

TABLE I

The incidence of side-effects in various representative series of cases.

Series	No of Cases	Average Dose (mg/day)	Percentage of Side-effects All	Major	Average Duration of Therapy
Boland (1950)	42	37 5–80 5	33	8 3	125 days
Polley (1951)	100	>75 0	63	?	Not stated
		<62 5	21	?	Not stated
Ward (1953)	46	49	20	0	15 months
Bilka (1951)	36	<100	25	10	5 months
Davison (1951)	19	<100	47	26	Not stated
Margolis (1951)	56	120 (ACTH)	50	23	225 days
Kuzell (1950)	19	62½	65	53	62 days
Levin (1953)	50	75	88	52	8 months
Ragan (1952)	59	large	100	36	10–12 months
Chase (1952)	7	massive up to 800	100	86	89 days
A R A. co-operative study (1954)	446	variable	72	46	> 2 years

The second table requires some comment since the numerical in-

(and their liability to perforate), osteoporosis and pituitary-adrenal suppression are common and important. On the other hand hypertrichosis, thrombophlebitis, headache, disturbed renal function and

bly due

begin-
ning of 1953 for the incidence of deaths associated with cortisone

4. As with any new drug, a host of incidental and probably un-
u
d
reported by Freyberg and his colleagues in New York in 1950, in which no less than 27 per cent. of all side-effects in a controlled study of chrysother

5. One of
is their relat
logical sense.
clinical sphere. Sometimes species or dosage differences may account for the different results obtained by different observers; but there seems to be something more fundamental than this.

It has been suggested for example that, in some obscure way, the response of a tissue to cortisone varies in relation to the particular metabolic state of that tissue at the time of administration, and its variable demands for the drug in relation to other tissues.

6. In any sober assessment of the side-effects of a drug the risks must be balanced against the severity and seriousness of the disease being treated. Thus for example, acne, hirsuties, and a moon-face, which are constant accompaniments of long-term steroid therapy, are high prices to pay for relief of pain in a young woman with a
ever far
one of
o think
clearly on this point has been responsible for much of the violent disagreement on the indications for these drugs

7. In general, the shorter the course the lower the incidence of side-effects, irrespective of dosage As the duration of treatment increases the level of the maintenance dose becomes of paramount importance in determining the incidence.

Incidence. The incidence of side-effects quoted in different long-term series varies literally from 100 to 20 per cent. and these prodigious discrepancies demand an explanation. The author has had personal experience of four long-term trials, two of which were done independently and two of which were part of large " co-operative studies." Even in these the published figures show marked discrepancies. To some extent this is merely a question of semantics and classification. For example, if every patient who manifested " mooning " of the face, a mild degree of euphoria, or a temporary menstrual irregularity was included as a case of " cortisone toxicity " it is certainly true that almost 100 per cent of cases would merit the description. Even when the
or " and " minor "
ence of opinion as

-operative study "
on, in which over
ent. " major side-
effects was reported in this study Since, however, the vague notation

explanation of the term "significant" is necessary It is not synonymous in this respect with serious, because a serious side-effect may be extremely rare while a mild one may occur routinely with cortisone. Significance implies that the side-effect has importance in the practical management of patients on cortisone Some of the relative or absolute contra-indications to cortisone in relation to its side-effects will also be touched upon, although these will be dealt with in more detail in a later chapter.

1. CARDIOVASCULAR

Hypertension. This occurs far less commonly than would be expected by analogy with Cushing's disease. It is said to be more common with ACTH than with cortisone. Often there is merely an initial rise followed subsequently by a return to normal. It is rarely sufficient to cause congestive failure It occurs more often in diseases where there is an associated renal lesion, such as disseminated lupus

exercised. Salt and water retention may lead to cardiac failure.

Other side-effects have been reported or might be expected on theoretical grounds, but their association with steroid therapy is largely unproven Thus *polyarteritis* is said to occur if cortisone is with-

A *bleeding* tendency has been reported, manifested by spontaneous ecchymoses, gastrointestinal hæmorrhage, hæmaturia and menorrhagia Finally, the development of *arterial spiders* is of great interest but of little practical importance

2 RESPIRATORY

Tuberculosis. The major fear is the spread of latent tuberculosis Routine pre-treatment chest X-rays are insisted upon in all reputable centres Relatively few cases of miliary spread have been reported in the literature and there is evidence that it requires a dose far in excess

than rheumatoid arthritis

therapy. At the time he could find records of thirty-two such cases, and of these only nine seemed to be directly attributable to the drug, whereas in the other cases the relationship seemed to be problematical or definitely coincidental. Of the nine whose death
four were due to pos
suicide in the course
does not claim this to
cases have been publis
the imagination can cor
which some authorities

TABLE II

The incidence of side-effects in a total of 510 patients extracted from various well-authenticated series.

Alteration in psyche	125	Decreased resistance to infections	8
Facial rounding	104	Headache	8
Fluid retention	96	Weakness	7
Hypertrichosis	46	Hypopotassæmia	7
Decreased glucose tolerance	39	Peripheral neuritis	7
Increased blood-pressure	36	Disturbed renal function	6
Acne	25	Striæ	6
Menstrual disorders	17	Aggravation of peptic ulcer	6
Tachycardia	16	Delayed wound healing	5
Supra-clavicular fat pads	13	Thinning of scalp hair	4
Ecchymoses	13	Arteritis	3
Sweating	12	Pigmentation	3
Excessive appetite or weight gain	11	Fractures (osteoporosis)	3
Thrombophlebitis	10	Temporary pituitary adrenocortical suppression	1
Aggravated menopausal symptoms	9		

The side-effects produced by the adrenal steroids and by corticotrophin are essentially similar in nature. Certain
differences, however, have bee
to produce more sodium and
tion, more acne, hirsutism, p
others. By contrast it produ
insufficiency when withdrawn.
water and salt retention, but are

Classification

In what follows the author has att
possible. Side-effects are class
this inevitably leads to some
cussed in detail, while others are mentioned for completeness Some

The significance of **renal glycosuria** lies not in its seriousness but in its recognition, since it explains the occasional glycosuria discovered in the course of routine urine testing and which is not due to the development of diabetes mellitus.

Azotæmia due to increased urea formation and potassium release has been reported as a cause of death, but is probably only relevant in extremely advanced renal disease.

5. SKIN

siderations they are seldom serious.

6 NERVOUS AND PSYCHIATRIC

Minor but common psychic reactions. Certain mild psychic upsets occur with considerable frequency with cortisone therapy They are relatively unpredictable and some even claim that they are merely

For example, we read of t
bath for the first time in
state of severe mania.

(ii) *Depression—Nervousness—Irritability* In this group the risk of impulsive suicide attempts must always be borne in mind

(iii) *Insomnia and alteration of sleep rhythm and motor activity.* All

acute toxic confusional states are the most common, although virtually any type of psychosis can occur. These conditions are considerably more common when the drugs are given for such diseases as

3. GASTRO-INTESTINAL

Peptic ulceration, perforated ulcers and hæmatemeses. The incidence of these complications is believed to be significantly increased by cortisone therapy and even more so by prednisone and prednisolone. This is denied by at least one authority who claims that there is a well-established relationship between untreated rheumatoid arthritis and peptic ulceration, and that these drugs have not altered this relationship. Some support for the latter view is given in a recent report of a series of known cases of peptic ulcer, some of whom were given ACTH and cortisone in order to compare the results with those having orthodox treatment without these drugs. No significant difference in healing times was noted

However, when ulcers do perforate, cortisone tends to obscure the *florid signs and symptoms, so that the diagnosis tends to be delayed,* and this is serious. Perforation may occur within a week of starting treatment or may be delayed for several months.

These are extremely important but quite unpredictable complications. Most people consider that any dyspeptic history is an absolute contra-indication to cortisone therapy. This seems to be an unnecessarily rigid view, although none would dispute that it is a *relative* contra-indication. The author has for special reasons, intentionally, given long-term cortisone to three patients with a definite history of peptic ulceration, without causing any ill effect. He has also seen cortisone-induced ulcers heal without discontinuing the drug when the orthodox therapeutic régime was introduced. It has been advocated that dietetic precautions, alkalies, antispasmodic drugs and other restrictions should be instituted routinely in any patient whose upper alimentary tract is suspect.

Flatulence and non-specific epigastric pain are regarded as significant merely because of their frequency, and because they may be a warning sign of peptic ulceration. They seldom necessitate stopping treatment,

4. RENAL

None of these is of great practical importance *Precipitation* of latent amyloid disease has been reported by two eminent authorities. The author considers the evidence to be extremely tenuous however, and indeed he has seen at least one case of established amyloidosis clear completely while the patient was receiving cortisone. Further study of this problem is undoubtedly required before the association is established

Fluid retention caused by increased tubular re-absorption may be significant though the extent to which this mechanism participates in the composite picture of fluid retention in any individual case is unknown

Azotæmia due to increased urea formation and potassium release has been reported as a cause of death, but is probably only relevant in extremely advanced renal disease.

5. SKIN

The incidence of significant skin lesions with cortisone and ACTH is reported as 16 per cent. Acne, hirsuties, striæ, ecchymoses and purpura are significant because of their frequency, and are the æsthetically unpleasing but almost inevitable manifestations of the "Cushing-like" syndrome produced by prolonged therapy Apart from cosmetic considerations they are seldom serious.

Urticaria, erythema multiforme and exfoliative dermatitis (responding to cortisone) have followed ACTH administration.

6. NERVOUS AND PSYCHIATRIC

Minor but common psychic reactions. Certain mild psychic upsets occur with considerable frequency with cortisone therapy. They are relatively unpredictable and some even claim that they are merely intensifications of normal personality patterns They range from the

For example, we read of the lady who, finding herself able to get into a bath for the first time in years, insisted on taking ten baths a day in a state of severe mania

(ii) *Depression—Nervousness—Irritability* In this group the risk of impulsive suicide attempts must always be borne in mind.

(iii) *Insomnia and alteration of sleep rhythm and motor activity.* All

acute toxic confusional states are the most common, although virtually any type of psychosis can occur. These conditions are considerably more common when the drugs are given for such diseases as

systemic lupus erythematosus, where there may also be organic involvement of the central nervous system by the disease process. It is always extremely difficult in these cases to know how much of the reactions should be ascribed to the drug and how much to the organic cerebral pathology.

It used to be thought that a predisposition was necessary before such diseases occurred, and, conversely, that the drugs should never be given to unstable personalities or patients with a history of previous psychotic or psycho-neurotic episodes Recent careful studies, however, emphasize the complete unpredictability of these reactions, and suggest that a suspect psychiatric background in no way precludes the future use of the drugs. Indeed, a patient who has a psychotic upset on one occasion, may have a completely normal response on the next, and vice versa. Many examples of this are quoted.

The psychodynamic aspects of this problem are considered by the psychiatrists at the Mayo Clinic to be an effort on the part of the psyche to maintain homeostasis in relation to (1) the pharmacological effect of ACTH and cortisone on the total organism; (2) the meaning to the patient of an alteration of the symptoms for which he was being treated; and (3) the nature of the patient's fantasies about the action of the substance he has been given

There is apparently no relationship between the intensity of the psychic reaction and the dose or the time for which the drug was given. The incidence of significant psychic changes in one series of 80 was 15 per cent and most of these were transient and mild in character.

Epileptic attacks have also been ascribed to these drugs, and they are undoubtedly related to the action of cortisone in reducing the convulsive threshold of the cerebrum. They may be major or minor seizures and are particularly likely to occur with the unstable electroencephalographic patterns seen in children The frequency of attacks in established epilepsy is also liable to be significantly increased unless covered by basal sedation

Peripheral neuritis, glaucoma, papillitis and optic atrophy, and [illegible] reported from time to time. The [illegible]

pathology underlying them is totally obscure.

7 ENDOCRINE

It is very common, when treating a patient with long-term cortisone therapy, to produce a syndrome which mimics hyperadrenalism or "Cushing's syndrome" very closely. In this state, the following manifestations are found to a greater or lesser degree:

(1) **Gain in weight,** which cannot be ascribed entirely either to the voracious appetite which the drug induces or to sodium retention.

(ii) **Deposition of excess fat** in the face ("moon face"), in the interscapular area ("buffalo hump") and in the supra-clavicular region

(iii) **Purplish "striæ distensæ"** especially on the thighs and abdomen.

(iv) **Acne vulgaris.**

(v) **Ankle œdema.** This is due partly to retention of sodium and partly, as already mentioned, to increased re-absorption of water by the renal tubules.

(vi) **Amenorrhœa** and other menstrual irregularities These are far less common than in the spontaneous condition of hyperadrenalism

(vii) **Asthenia** and muscular weakness

(viii) **Diminution of libido.**

(ix) **Spontaneous ecchymoses.**

(x) **Osteoporosis** and pathological fractures.

(xi) **Hypertension,** which is considerably less frequent than in the natural syndrome

(xii) **Hypertrichosis.**

(xiii) **Development of insulin resistance** and of diabetes mellitus (*vide infra*) Here it will suffice to note that the cortisone-induced condition seldom, if ever, gives rise to a significant degree of ketonæmia or ketonuria

(xiv) **Gynæcomastia.**

(xv) **Erythrogenesis.** Unlike the spontaneous condition in which its incidence is between 10 and 33 per cent of established cases, polycythæmia is not an important feature of iatrogenic Cushing's syndrome

Adrenal atrophy.

A *Temporary* A second group of significant endocrine side-effects is associated with the temporary—but usually reversible—atrophy of the adrenal glands which follows long term therapy ...

such manifestations as extreme muscular weakness, hypotension, nausea, water and sodium diuresis, and occasionally a rather dramatic

happens There is some doubt as to whether the giving of corticotrophin to stimulate the atrophic adrenal gland has any beneficial effect in practice Histologically it appears to be the zona fasciculata and recticularis which atrophy most, the zona glomerulosa remaining practically unaltered.

B *Irreversible* Although there is evidence of some return of adrenal function within a few days, this probably does not resume complete normality for several months The evidence for this statement is culled from a few well authenticated and highly disturbing cases Some

patients, following a period of cortisone therapy have been subjected to a relatively minor stress such as a small operative procedure within periods ranging up to eighteen months from leaving off the cortisone. They have suffered from an inexplicable, and often fatal, acute adrenal failure.

It is recommended that this contingency should be anticipated by warning the patients of the risks, and by following the practice of the Mayo Clinic who ensure that all patients carry a card on their persons, which reads as follows:

TO WHOM IT MAY CONCERN

> This patient........ .... has been receiving cortisone for rheumatoid arthritis. This treatment suppresses adrenal-gland function. In case of accident involving severe injury, bone fracture, shock, &c. (with or without the need for emergency surgery) the use of extra cortisone* may be imperative, even life-saving Medical programs for such emergencies have been published: Sprague *et al.*, J.A.M.A., Feb 21, 1953; Ward *et al.*, J.A.M A , May 9, 1953.

Diabetes Mellitus. The diabetogenic effect of corticotrophin was discovered experimentally as early as 1941. On the basis of this experimental evidence, diabetes is a surprisingly less common complication of steroid therapy than might have been expected It is reversible in nearly every case after the drug is withdrawn, providing that it has not been present too long

Its occurrence is unpredictable, and positive family histories of diabetes or abnormalities of glucose tolerance before treatment commences do not seem to be of any help in anticipating it. In a patient who already has diabetes and also rheumatoid arthritis, the diabetes represents only a *relative* contra-indication to cortisone therapy because, although the insulin requirements will considerably increase, serious complications of the existing diabetes do not arise.

The incidence of diabetes has been computed at 1 [illegible] 500 cases

It happens that the author has seen a disproportionately high incidence of this condition in his experience It has been possible in every [illegible] cortisone therapy

From a practical point of view the patient's urine should be tested weekly in the early stages of treatment, and certainly never less than once a month at any time. If glycosuria occurs the next problem is to determine whether it is merely a renal glycosuria or a true manifestation

* Or one of its potent analogues

of the diabetic state. Simultaneous blood and urine estimations and a glucose tolerance curve will solve this problem quite simply.

It has been argued that since ketosis is not a common complication of this form of diabetes, and since the patient is usually symptom-free, it is unnecessary to try to control the level of blood sugar rigidly.

Having discussed this with many diabetic specialists, the author has come to the conclusion that this is a fallacious point of view. Latent complications of diabetes such as peripheral neuropathy, atherosclerosis and retinopathy, appear much sooner in those cases of diabetes in whom the level of the blood sugar has not been kept under strict control.

In spite of the inconvenience, therefore, it is recommended that if a patient who develops diabetes is to be kept on cortisone therapy he should have simultaneous injections of insulin, and sometimes extremely large doses are needed in order to bring the blood sugar to normal levels. He should also submit to dietetic restriction of carbohydrate and calory intake.

indication for reviewing the case carefully to see whether the hazards and inconveniences of cortisone therapy are really justifiable. If, after a careful balance of the pros and cons, it is still considered that the patient's arthritis would suffer by withdrawal of the cortisone, the author has no hesitation in recommending that the treatment should continue.

Although some degree of *hypothyroidism* is said to occur in up to 80 per cent of patients on long-term cortisone, the condition generally remains sub-clinical. The evidence is usually based on laboratory tests such as a lowered basal metabolic rate, hypercholesterolæmia, reduction in the serum protein-bound iodine and a diminished radio-iodine uptake by the thyroid

Some centres recommend routine thyroid administration when using long-term cortisone therapy, but we have not found this necessary. Occasionally, if cortisone is stopped too suddenly, a latent thyrotoxicosis may develop. Very rarely a true thyroiditis results from prolonged treatment

patients, following a period of cortisone therapy have been subjected to a relatively minor stress such as a small operative procedure within periods ranging up to eighteen months from leaving off the cortisone. They have suffered from an inexplicable, and often fatal, acute adrenal failure.

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The incidence of diabetes has been computed at 1 500 cases

It happens that the author has seen a disproportionately high incidence of this condition in his experience It has been possible in every case to maintain the patients symptom and sugar-free by administering very large doses of insulin, with appropriate dietetic restriction Nevertheless experience has made him regard this as a major hazard of cortisone therapy

From a practical point of view the patient's urine should be tested weekly in the early stages of treatment, and certainly never less than once a month at any time. If glycosuria occurs the next problem is to determine whether it is merely a renal glycosuria or a true manifestation

* Or one of its potent analogues

9 MISCELLANEOUS

(i) **Impaired Wound Healing.** The risk of this complication was given excessive publicity in the early days of cortisone therapy largely on the basis of animal experimental work.

Two common errors of interpretation were evident in this work. Firstly, the effect on wound healing appears to some extent to be species specific and illustrates the danger in clinical research of arguing by analogy. For example, the original experiments were done on the ears of rabbits. Attempts to repeat them on guinea-pigs and dogs were entirely unsuccessful In the case of human biopsy material the results were very inconclusive. Secondly, the doses used in the original experiments were vastly in excess of those which one would contemplate using clinically, on a weight-for-weight basis.

Our considerable experience of this problem suggests that it is per- [illegible]

edges especially carefully before the sutures are removed Some surgeons, in deference to the potential risk, make a habit of leaving in their sutures routinely for a few days longer than is customary

(ii) **Pathological fractures, secondary to osteoporosis.** The catabolic effects of cortisone on the nitrogen and calcium metabolism have already been discussed The risk that this might lead to generalized osteoporosis of the skeleton resulting in fractures was soon appreciated Sometimes these were apparently spontaneous, others resulted from minimal stresses

[illegible]

stimulated by the patient's sudden loss of pain and stiffness

The threat of this very serious complication must always be in the forefront of the physician's mind when selecting a case for long-term steroid therapy, otherwise he will find that many of his patients will merely exchange their light corrective rheumatoid splints for the [illegible]

senile rheumatoid arthritics who might otherwise obtain substantial relief from the use of the drug It should provide a considerable incentive for the steroid chemist to modify the structure of cortisone so as to overcome this complication as successfully as he has recently overcome its sodium-retaining propensities

When fractures do occur, it is usual to reduce the dose of cortisone to facilitate the speed of healing. The author has, however, seen two

cent. increase in extracellular volume and plasma volume. However, whilst this is the typical response, enormous individual variations exist.

Some claim that by giving about 200 m.equiv. of potassium per day to a patient, a pronounced diuresis will occur and this may even enable a waterlogged patient to continue therapy. Similarly mercurial diuretics may be used in such patients, but this is not free from risk, and it is recommended that whenever they are used *supplementary* potassium should be given at the same time to prevent the risk of hypokalæmia. Another approach to the problem has been ion exchange resins. However, these are unpleasant to take and it is extremely difficult to estimate the dose accurately, consequently they have found little general application.

Low-sodium diets are prescribed routinely in many clinics. However most people have the impression that they are ineffective unless extremely stringent (i e., less than 200 mg. of sodium daily). As this is an extremely unpleasant and often impracticable diet, it is generally reserved for those cases with an inherent tendency to retain fluid while taking the drugs. This particular hazard has of course been greatly reduced by the advent of the new drugs, prednisone and prednisolone.

(ii) **Hypokalæmia.** This complication was predicted on theoretical grounds in the very early days of cortisone treatment. Consequently [illegible]

ser [illegible]

[illegible] minor to [illegible] graphic methods do occur. This statement is made on frankly empirical grounds, because of the frequency with which such symptoms as apathy and physical exhaustion will improve if supplementary potassium is administered

One complication of this hit or miss approach has been reported, namely that a patient who was given potassium for mild hypokalæmic alkalosis developed severe tetany. It is also unsafe to give large doses of potassium to a patient with poor renal function in the absence of strict laboratory control

(iii) **Nitrogen and Calcium Metabolism.** As with sodium, so with nitrogen and calcium, there are generally three distinct phases The balance is almost invariably negative for the first ten days, it then frequently becomes positive for the next three weeks and only becomes negative again finally between the thirty-fifth and forty-fifth day and thereafter

The clinical significance of this is in the production of spontaneous fractures and the failure of wound healing (*vide infra*) Efforts have been made to reverse the negative nitrogen balance by giving large doses of testosterone at the same time as the cortisone These are frequently successful, but they are often not practicable, especially in women.

to cortisone from time to time, and, whilst theoretically possible, the evidence that it was more than a coincidence has usually been unconvincing and the resulting morbidity not very severe.

Certain minor miscellaneous side-effects remain to be discussed

(i) **Effects on the fœtus.** One of the last "complete taboos" about cortisone therapy to disappear was its administration to the pregnant woman. This was not a serious drawback, however, as by the very nature of the disease for which it was being commonly used it often became unnecessary.

babies treated with ACTH and cortisone for retrolental fibroplasia fared very badly indeed. However it was pointed out in an editorial in the *Journal of the American Medical Association* that the doses used in these experiments were greatly in excess of normal clinical dosages so that no definite conclusions should be drawn

In 1952 a series of five cortisone-treated pregnancies was published, as a result of which the authors concluded "... It would appear that cortisone can be administered when necessary to pregnant women." The comparison between humans and animals was further reviewed in an annotation in the *Lancet.* Since then the pendulum has swung

ception in cases of relative infertility.

(ii) **Secondary severe foot strain.** When a bedridden arthritic patient suddenly becomes ambulant, the additional strain on his feet may produce a secondary pain of mechanical origin almost as severe as the original inflammatory pain. In order to anticipate this it is now customary to give routine faradic foot-baths and exercises to all bedridden cases before they start on the drug

(iii) **Cortisone-induced gout.** This is a rare curiosity of considerable theoretical interest Cortisone normally reduces the blood uric acid and dramatically resolves an acute attack of gout. However, it often gives rise to an even more acute "rebound" attack while it is being withdrawn and it is therefore not considered to be practical therapy.

ADDICTION, RESISTANCE AND HYPERCORTISONISM

fractured necks of femora heal with perfectly strong callus formation whilst the patients continued to take 100 mg. per day.

tonitis or a widespread pneumonia with minimal signs, symptoms or constitutional reactions.

Many tragedies have occurred unnecessarily because clinicians have not been aware of this hazard. In other cases the clinician has not

and alertness to unsuspected dangers. There is no proven evidence that, when the underlying pathological condition is recognized and correctly treated at an early stage, cortisone therapy *per se*, will influence the prognosis adversely. Indeed some intrepid workers use these steroid drugs routinely in order to *control* the inflammatory responses in such conditions as perforated peptic ulcers and other forms of peritonitis.

The moral quite simply is that every incidental complaint of a patient on suppresive doses of cortisone must be very carefully investigated, and the traditional diagnostic criteria of the textbooks should be forgotten—or at least considerably modified. When a diagnosis is made,

taken early enough, and an emergency arises, it may be necessary to

cases he has followed in detail, the objective deterioration following dose reduction has invariably been far less than the subjective.

A point against this interpretation, however, is the observation that such a patient may respond both objectively and subjectively to a change to one of the other steroids Thus a patient who is doing poorly on cortisone may show a gratifying improvement if he is changed on to hydrocortisone, or more recently prednisone.

In the case of corticotrophin, by contrast, there does seem to be more evidence, both clinical and experimental, that a true resistance can develop. This is more reasonable since corticotrophin is a foreign protein. However, careful search for the presence of antibodies in these cases has usually revealed no evidence that they are the responsible factor.

[illegible] covered except for the observation that when a patient becomes re- [illegible]

venously.

Hypercortisonism. Slocumb used this term for a syndrome which occurs relatively late in therapy in those patients who develop suppression of adrenal and pituitary activity They are unable to respond to stress by producing more endogenous cortisone But their tissues are so attuned to a high level of exogenous cortisone that if requirements temporarily increase (e g , due to stress) or if a dose is delayed, they develop characteristic symptoms. These consist of an apparent flare in the patient's condition.

Superficially this might appear to be merely an exacerbation of the arthritis, but if carefully analysed the pains are diffuse and not localized to the joints

Accordingly " muscular aching," " exhaustion " and a feeling of depression are the characteristic descriptions These complaints are usually cyclical and are interspersed with periods of restlessness and excessive energy. The joints show no objective evidence of increased synovitis, and it is the muscles rather than the joints which are acutely tender, the patient often exhibiting the " touch me not " phenomenon. He will often feel better after a rest as opposed to the " jellying " complained of characteristically by the rheumatoid patient, conversely, exercise will generally make him feel worse. Heat, physiotherapy and analgesics are poorly tolerated and do not relieve the symptoms

Each individual dose of cortisone will cause a temporary relief in the symptoms followed by a flare. By contrast, if the patient is on an inadequate total daily dose he is unlikely to get relief from any individual instalment. If the total dose is increased, the true " Rheu-

drug, on which he claimed to be totally dependent. What is far more common, and often mistakenly called "Addiction" is the anxiety with which some patients oppose any suggested reduction in their dosage, and the extreme terror with which the inevitable "withdrawal symptoms" are greeted. It is certainly a mistake to confuse this with true addiction since such patients, if properly handled and if sufficiently intelligent, will nearly always co-operate with the physician when they realize that the dosage reductions are for their safety and ultimate benefit

It could legitimately be argued that this is the manifestation of a natural reaction of a sufferer who is determined not to lose the ecstasy associated with sudden freedom from pain and stiffness. Certainly it was a more serious problem in the early days when very high initial dosages were the rule.

Primary cortisone resistance. This is a well-recognized but very rare phenomenon in which a patient with active disease may show no subjective or objective clinical response to cortisone even when the dose is raised to three or four hundred milligrammes a day.

The explanation of this resistance is completely obscure, especially since the same patient may be reasonably sensitive to hydrocortisone or corticotrophin It would be tempting to speculate that hydrocortisone is the natural and active hormone, and that certain people lack the enzyme which converts cortisone to hydrocortisone Technical limitations in the field of enzymology have so far precluded any serious research into this phenomenon, but it may hold an important clue for the future

Acquired resistance. This is a subject which has been discussed remarkably little in the literature, despite its obvious importance and the fact that most clinicians tacitly agree that there is a perceptible falling off of clinical response in many cases after cortisone has been administered for two or three months, even with constant dosage.

Sometimes, however, this deterioration may be precipitated by a premature lowering of the dose. Following this, it seems that the earlier status frequently cannot be regained despite a return to (or even above) the original dose. Again, temporary resistance may be caused by such factors as emotional upsets, intercurrent infections, trauma from over exertion, changes in the weather, and alterations in responsiveness of the endocrines.

No satisfactory explanation of the apparent "tissue habituation" has been advanced and its experimental basis is extremely tenuous. Some have even argued that it is fictitious and a delusion They suggest that the initial improvement gives rise to disproportionate euphoria, and that it takes some time and the inevitable reduction of dosage to a safe maintenance level before the patient's psyche stabilizes He then

people have for past suffering could account at least for the subjective aspects of the relapse.

The author largely agrees with this point of view as, in most of the

cases he has followed in detail, the objective deterioration following dose reduction has invariably been far less than the subjective.

A point against this interpretation, however, is the observation that such a patient may respond both objectively and subjectively to a change to one of the other steroids. Thus a patient who is doing poorly on cortisone may show a gratifying improvement if he is changed on to hydrocortisone, or more recently prednisone

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matoid flare" will benefit, whereas the hypercortisone patient will get a very temporary improvement followed by a further distinct deterioration.

The memory of these patients tends to be slow or impaired and they

commencing the

are much more common in post-menopausal females than in other groups, but may occur in anyone.

It is naturally of supreme importance to recognize this syndrome and not to mistake it for a flare in the disease since the treatments are diametrically opposed to each other.

The treatment of a true flare is to adjust the dose accordingly until it settles down again. To do this in hypercortisonism would merely be to perpetuate a vicious circle and make the tissues even more dependent

2·5 mg. per day, and even then he is content to wait a day or two between each decrease while the inevitable flare settles down. This is a tedious but ultimately rewarding process, and any attempt to hurry it will probably make the patient feel extremely ill. In this country we have

clinic group, but it is not universally accepted as an entity by other authorities It is certainly an extremely ingenious explanation of a commonly observed phenomenon, and it provides some explanation and a logical therapeutic approach to a proportion of those cases previously labelled " Acquired cortisone resistance "

Conclusion

In the introduction to this chapter it was stated that it was intended

not to what Hench has termed a " Happenstance " Hench's neoligisms are always graphic, and on this occasion he was referring with some

population For example, one of our patients who was doing particularly well on cortisone, suddenly dropped down dead. A post-mortem examination revealed a massive cerebral hæmorrhage emanating from a small berry aneurysm on the Circle of Willis. The pathologist who carried out the autopsy assured us that by no stretch of the

imagination could such a catastrophe be due to the therapy. Nevertheless we had, for the sake of accuracy to record the death when we published our series, and there is little doubt that this is the type of case which figures in many of the review articles which are published from time to time without any effort to view the problem critically and in perspective.

The presentation and interpretations of these complications must to some extent be coloured by personal experiences and prejudices. In spite of all efforts to minimize this bias, there will doubtless be readers who will criticize the apparent levity with which some of the complications are described, as compared, for example, with the rather portentous descriptions of diabetes and stress fractures. However prejudiced they may be, they represent our considered views of the relative dangers of the drug after eight years' continuous use.

CHAPTER 4

THE PRACTICAL PROBLEMS OF CORTISONE THERAPY

SINCE most of the " practical problems " are associated ultimately with the risks of undesirable side-effects, this chapter must be read in close conjunction with Chapter 3.

I. *Case Selection*

" *The absence of contra-indications to cortisone therapy does not necessarily imply that it is indicated* "

[illegible] between the therapeutic and the toxic dose. Its importance is also [illegible] already seen, sometimes the problems connected with its withdrawal are more serious than those connected with its administration.

It is particularly frustrating, therefore, to have to report that after eight years' experience there is no unanimity amongst the experts on this subject, there is not even a satisfactory, authoritative statement from amongst them to guide the novice.

However it is obvious that in attempting to be dogmatic in classifying the purely-medical indications for therapy it is necessary to take into account the pharmacological unpredictability of the steroids and individual idiosyncrasies in dosage requirements. It is also extremely important to evaluate non-medical factors such as social and occupational necessity, the personality and intelligence of the patient, etc. Even when all variables are taken into account, the selection of an individual patient for steroid therapy is still something of a gamble. Therefore to every rule enunciated below, one could find well-authenticated exceptions to belie it.

For example, desperate problems frequently beget desperate remedies [illegible]

not rigid rules.

A. Absolute Indications

(i) **" Fulminating " Rheumatoid Arthritis.** Included in this description are those, fortunately rare, cases in which disease starts suddenly and which proceed rapidly but inexorably downhill so that they become crippled within a matter of weeks (sometimes even days).

It is said that these are the cases which ultimately have the best prognosis This also accords with our experience, if by " prognosis " one is referring only to liability to remission However, many of these patients will have suffered irreversible joint damage with deformity and ankylosis before the remission occurs

It is our firm contention, that although cortisone therapy will have no effect on likelihood of remission it will probably enable the mobility of the joints to be maintained until this occurs It is therefore quite justifiable to use doses in excess of those customarily recommended for [illegible]

[illegible] cachexia, fever and other signs of constitutional disease. The small death-rate of rheumatoid arthritis is largely drawn from this group. Those who escape this ultimate penalty may suffer from permanent ill health even after the " fire " of the disease is burned out. The pathogenesis of this is obscure but it may be due to early amyloid changes It is our impression that such cases recover far more completely and rapidly if the acute phase of the disease is covered with steroid therapy This impression, however, lacks statistical authenticity because of the relative scarcity of this type of case.

B. Relative Indications

(i) **Rheumatoid arthritis in children.** It has been argued that children require relatively enormous doses of the drug and that this is an unjustifiable risk. Our experience suggests the reverse and that whilst [illegible]

[illegible] effects are considerably less [illegible]

[illegible] bed rest in hospital.

(iv) **Arthritis Mutilans,** in which all our efforts must be directed towards prevent [illegible]

[illegible] changes

[illegible]

resemble subacute disseminated lupus erythematosus. They are also the group which seem to develop amyloid disease. We believe that suppressive therapy with cortisone *may* delay both these complications.

(vii) **Stiffness.** Cases in whom stiffness is a predominant symptom, and as a corollary of this·

(viii) ***Disproportionate Functional Disability.*** Where functional [illegible]

[illegible]

feature, especially if these are of recent origin.

(x) **Psychological Factors.** When a patient's disease is obstinately static, and he is of low morale and intolerant of chronic invalidism, it is sometimes justifiable to use the drug to boost morale or as an aid to rehabilitation if no obvious contra-indications exist. Sometimes if the risks are presented honestly to such a patient he will elect to take them rather than remain an unhappy and useless cripple. As a corollary of this.

(xi) **Economic and Social Factors.** It may be an economic or sociological necessity for a patient to remain in employment, or at least self-sufficient. This is a situation which can occur even in our Welfare State (for example the case of the young mother without adequate help for her children) It is of far greater significance in countries such as the United States where social insurance is less advanced and economic pressures far greater than in this country

Here again the physician owes it to his patient to try to evaluate the risks for him, and to explain that in his case it is a trial and error procedure whose chances of success will be increased by his co-operation in cutting down his physical and mental stresses to a minimum.

(xii) **Intelligence and Stability.** Finally, when selecting a case for cortisone therapy we pay particular attention to the patient's intelligence and stability This will increase the likelihood of his co-operating effectively in the process of finding his correct maintenance dose, which *is frequently tedious and frustrating*

This dose will need to be adapted frequently to the vicissitudes which [illegible]

diabetic

C. Absolute Contra-Indications

(i) **Active, or recently active Tuberculosis.** This is classified as an "absolute contra-indication" in deference to orthodox teaching and

because the author has had no personal experience with which to refute it.

However, it is possible to conceive of situations where the risk would be justifiable if covered by streptomycin and para-amino-salicylic acid. Indeed there are investigators who claim that cortisone is actually a useful drug in the management of tuberculosis, since it enables the antibiotics to gain better access to the invading organisms

However until this somewhat unorthodox approach is substantiated, it is safer to regard phthisis as a major hazard of steroid therapy to be avoided, save in exceptional cases.

(ii) **Primary Resistance.** Total failure to respond to cortisone is a well-established phenomenon It is said to occur in 10 per cent of cases Naturally it precludes altogether the use of this drug; although —as described elsewhere—such cases may be surprisingly responsive to other drugs in the steroid group

" Relative cortisone resistance," by contrast, can be of all degrees; and it is a factor to be considered in every case when assessing the prospects for successful therapy. Unfortunately there seems to be no

D. Major, but Relative Contra-Indications

ain is included largely in recent work has cast con-

This work, carried out at the Maudsley Hospital and corroborated independently by American investigators, concluded that cortisone-induced psychoses do not depend to any measurable extent on the pre-existing personality patterns and are not even influenced greatly by a history of a previous mental breakdown Indeed, they found that a patient might develop a severe psychosis on one occasion when he receives the drug, and be perfectly all right on subsequent occasions

elsewhere)

(iv) **Generalized Osteoporosis.** *We regard this as such a serious* hazard that it is at least debatable whether it should not have been included as a " complete contra-indication ". The decision not to do so was made largely because of the difficulties of defining and classifying

and severity of

...ase in weight by its effect on the appetite, by causing sodium retention and by shielding

the body from some of the factors which normally cause cachexia. If the patient is already obese before therapy commences complications are liable to ensue, and these patients in practice seldom tolerate the drug well. They frequently complain of an uncanny feeling of being bloated. The additional strain imposed on the arthritic joints is another reason why these patients do badly.

E. Minor Contra-Indications

(i) **Cardiovascular Insufficiency,** including myocardial insufficiency with or without coronary atherosclerosis, or a tendency to thrombo-embolic phenomena.

(ii) **Renal Insufficiency.** This is included largely on the basis of animal experimental work. It is not usually a very significant hazard in practice.

(iii) **A pre-existing severe degree of Hypertension,** which may be exacerbated by cortisone, leading to the risk of cerebro-vascular accidents or heart failure.

(iv) **Climacteric.** Menopausal and, to a lesser extent, post-menopausal females tolerate these drugs notoriously badly.

(v) **Hysterical Personalities.** Cases in whom a hysterical overlay causes symptoms which are disproportionate to the objective signs Such cases are usually difficult to control, they constantly demand higher doses and refuse to co-operate in necessary dosage reductions. [illegible] e drug which, [illegible] that word, is [illegible]

(vi) **Economic Factors.** In those cases in whom financial, or other non-clinical factors might force a premature withdrawal of the drug This risk is naturally becoming less prevalent as the drugs become easier to obtain and cheaper. However we have seen sufficient tragedies from [illegible]

It would be pleasant if one could weight these various indications [illegible]

faulty selection of cases.

2. Laboratory Aids to Cortisone Therapy

In the last section, we reviewed the clinical problems which arise in selecting cases who are likely to respond well to steroid therapy; it

problems.

(1) Case selection.
(2) Drug selection.
  (*a*) The right drug for the right patient.
  (*b*) Screening of new drugs.
(3) Maintenance dosage.
(4) When to stop treatment

(1) The clinical problems of case selection have already been dis- [illegible]

Insulin Tolerance Test in diabetes Conversely one might learn from experience that certain *empirical* tests indicate the likelihood of a good response

One can say straight away that the realization of these ideals is almost as far away from fulfilment now as it was in 1948 The published work [illegible] gently instead of intuitively.

(2) In using the term "Drug Selection" we have two problems in mind:

(*a*) In the first place, our choice of which particular steroid to use in any given case is purely empirical at the moment It rests to some extent on which one is most easily available, but largely on the personal predilection of the physician in charge of the case.

There is no doubt that some patients respond better to one drug than another It would be extremely useful to have an objective test by which we could detect such differential sensitivity before treatment commenced and not by trial and error methods as at present. Here again we are forced to confess that there has been no notable progress since 1948

(*b*) At the moment there are no tests whereby a new drug for which anti-rheumatic properties have been claimed can be screened, save by the laborious and expensive process of clinical trials. We badly need a laboratory test which correlates specifically with the degree of rheumatoid activity. When we have such a test we may legitimately

envisage running a diabetic clinic without the benefits of tests for glycosuria and the level of the blood-sugar, or the administration of anticoagulants without facilities for measuring the prothrombin index. Quite a large volume of research has been published on this aspect of [illegible]

[illegible] sion been induced or occurred spontaneously?

This is no mere problem of academic interest, for the premature withdrawal of the drug based on a false interpretation may result in a severe flare of the disease process It is usually difficult to control this even if [illegible]

Even [illegible]
gradual [illegible]
confour [illegible]
certain [illegible]
followed by a temporary recrudescence of symptoms, even if the disease is basically inactive. It is quite easy to mistake these symptoms for a true flare of the rheumatoid arthritis unless one is aware of this phenomenon An incorrect interpretation may lead to a further long period of fruitless therapy before the experiment is tried again Here at least we have a few hints that some of our tests which respond—but respond obstinately—to cortisone might prove useful when they are properly classified

[illegible]

the physiological and pharmacological properties of these drugs, since most of them were devised on the basis of one or more of these properties.

A. Traditional Tests associated with Rheumatoid Arthritis

(i) The Erythrocyte Sedimentation Rate. This time-honoured, moderately reliable and simple method of assessing the degree of activity of the rheumatoid process becomes an unreliable guide during cortisone therapy Almost constantly there is an initial dramatic response Even this, however, is partially spurious since cortisone influences *directly* some of the factors which govern the height of the sedimentation rate The fall may therefore be independent of its effect on the "rheumatic" process

Following the initial drop, this index generally remains low for a few weeks, and then frequently shows a marked tendency to escape. This escape may be related to a reduction of dosage or it may occur for no apparent reason. Thereafter the ESR tends to remain elevated

permanently, even if the patient goes into a complete remission It therefore becomes a completely useless index of disease activity at this point.

[illegible]

is a temporary one, and is usually followed by a shift in the reverse direction which may even exceed the original one Finally an equilibrium is established The level of this equilibrium is determined by several factors quite unrelated to the activity of the patient's disease.

Within a week or ten days the results of a second and more relevant phenomenon become manifest, namely a true erythropoiesis It is clear that an index which depends on the interplay of two such unrelated factors is likely to represent neither the degree of inflammation of the rheumatoid tissues nor the requirements of cortisone to overcome it

[illegible]

[illegible] does not return quickly to normal if a patient goes into remission Therefore it can neither be applied to the problems of dosage requirements nor to the early recognition of remissions. There is however some recent evidence that [illegible] the [illegible] tions [illegible]

B. New Tests based on known Physiological Actions of Cortisone

(1) The Eosinophil Response. This test was based on the observation that following the administration of corticotrophin—and to a lesser extent cortisone—there was a rapid and consistent fall of circulating eosinophils to at least 50 per cent of their original number Sometimes they disappeared altogether. It seemed that this might be a ready-made test, suitable for grading responses to the drug and indicating its [illegible]

deficiencies.

[illegible] tests for gly-
[illegible] ration of anti-
[illegible] ombin index.
[illegible] been published on this aspect of [illegible] being solved yet.

[illegible]

pression of a condition which remains basically active, or has a remission been induced or occurred spontaneously?

This is no mere problem of academic interest, for the premature withdrawal of the drug based on a false interpretation may result in a severe flare of the disease process It is usually difficult to control this even if the drug is recommenced at the original dosage.

Even the cautious clinician who tries to solve the dilemma by a *gradual trial reduction of dosage is liable to make "confusion worse confounded".* It is notorious that the tissues become habituated to a certain level of circulating steroid, and any reduction is likely to be followed by a temporary recrudescence of symptoms, even if the disease is basically inactive. *It is quite easy to mistake these symptoms for a true flare of the rheumatoid arthritis unless one is aware of this phenomenon* An incorrect interpretation may lead to a further long period of fruitless therapy before the experiment is tried again. Here at least we have a few hints that some of our tests which respond—but respond obstinately—to cortisone might prove useful when they are properly classified

Despite our continuing difficulty in dealing with these problems, it would be profitable to summarize some of the negative evidence which [illegible]

[illegible]

properties.

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[illegible]

no apparent reason Thereafter the ESR tends to remain elevated

permanently, even if the patient goes into a complete remission. It therefore becomes a completely useless index of disease activity at this point

(ii) **The Hæmoglobin and Red Cell Count.** The degree of anæmia has traditionally been accepted as a rough index of disease activity in cases of rheumatoid arthritis, but like the sedimentation rate it also gives

direction which may even exceed the original one. Finally an equilibrium is established. The level of this equilibrium is determined by several factors quite unrelated to the activity of the patient's disease.

Within a week or ten days the results of a second and more relevant phenomenon become manifest, namely a true erythropoiesis It is clear that an index which depends on the interplay of two such unrelated factors is likely to represent neither the degree of inflammation of the rheumatoid tissues nor the requirements of cortisone to overcome it

to normal if a patient goes into remission Therefore it can neither be applied to the problems of dosage requirements nor to the early recognition of remissions. There is however some recent evidence that patients with negative tests have a better prognosis, even though the disease may appear clinically very active Exactly the same objections apply in the case of the hæmolytic streptococcal agglutination test.

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There can surely be no clinical applications of a test with so many deficiencies.

(ii) **The Lymphocytic and Leucocytic Responses.** Cortisone produces a marked lymphopænia and a moderate leucocytosis within two or three days of its administration Accordingly several workers attempted to use serial differential white blood counts for the purposes we have enumerated. It is, however, so crude an index as to be virtually only a qualitative measurement, and the only use we make of it to-day is in the negative sense, i e., if it does not occur, in any given case, we suspect either that the patient is abnormally resistant or that the dosage he is receiving is too low

(iii) **The Uric Acid: Creatinine Ratio.** Cortisone has a well-recognized uricosuric action It probably acts by increasing the clearance through the renal glomeruli It also has a definite but much smaller effect in increasing the excretion of creatinine. The constant rise in the ratio of these two substances in the urine was used as a relatively simple measure of the metabolic response to the drug. It was soon discovered that whilst the initial response was constant, the subsequent results depended on many irrelevant factors such as the size of the " miscible pool " of uric acid, and it has been abandoned as a useful clinical test.

(iv) **Differential Analysis of the Plasma Proteins.** In rheumatoid arthritis there is a tendency for a reversal of the normal albumen : globulin ratio and a marked rise in the plasma fibrinogen In the globulins, the greatest changes are in the alpha-I, the alpha-II and the gamma fractions. Adequate suppressive therapy with cortisone always results in a tendency for these anomalies to revert to normal.

They do so at different speeds, and the alpha-II fraction in particular behaves very obstinately compared to the others Chemical methods of estimating all these fractions are too laborious to be used as a routine, but it is possible to follow the relative changes very accurately by electrophoretic methods.

We have not yet applied these methods to sufficient cases to be sure of their clinical value. It seems to be a line well worth following, particularly in relation to the alpha-II fraction, which, by virtue of its obstinacy, may be more specific than the others. There are biochemical methods which purport to measure this fraction alone, and at least one American worker has claimed that they are of considerable value in assessing disease activity.

Reverting to our original criteria for these tests, plasma protein studies are unlikely to help in case selection. They could conceivably be of assistance in " screening " untried drugs, they are probably too inaccurate and cumbersome for routine use in solving problems of dosage, but might well be of considerable help in the final problem of differentiating real from drug-induced remissions

Further investigation of this group is undoubtedly strongly indicated, and recent publications suggest that several clinical research groups are currently interested in it.

(v) **Liver Function Tests.** Many of the routine liver function tests are found to be abnormal in active rheumatoid arthritis. The anomalies seem to be quite non-specific, and probably depend on the abnormalities of the serum globulins which have been discussed in the last section. These liver function tests do return to normal in most cases on

(vi) **Urinary Amino-Acid Studies.** These are included in this survey, not because they have in any sense reached the stage of a routine

In brief, Holbrooke and his group in Texas have described variations from the normal in the pattern of amino-acid excretion which seem to be specific for rheumatoid arthritis. These anomalies show a distinct tendency to revert to normal in natural remissions, in pregnancy-induced remissions, and in remissions induced by cortisone.

Robinson and his group at Ann Arbor went one stage further and pointed out that whilst cortisone and corticotrophin possess this property, corticosterone had no effect whatsoever. Now it has been pointed out elsewhere that corticosterone (Compound B) has virtually all the metabolic properties of the therapeutically active steroids but none of its " anti-rheumatic " potency. It does seem therefore as if the amino-acid metabolism and its anomalies might be " tied " specifically—in some obscure way—to the degree of inflammatory activity. It is certainly premature to make any claims of this nature, but it is at least a subject which calls for further study, and if the above results are confirmed, it represents a challenge to the chemists to devise simpler methods of measurement so that it can become a routine test.

C. Steroid Studies

The study of steroid biochemistry naturally received a profound fillip from the discovery of the therapeutic potency of cortisone.

arthritis then *ipso facto* there must be either an anomaly or at least

The other main line of research was the study of the metabolism and excretion patterns of these substances when administered systemically in the grossly unphysiological doses necessary in therapeutics

The first problem can be dispensed with speedily by stating categorically that despite a vast amount of research no proven evidence

(ii) **The Lymphocytic and Leucocytic Responses.** Cortisone produces a marked lymphopænia and a moderate leucocytosis within two or three days of its administration. Accordingly several workers attempted to use serial differential white blood counts for the purposes we have enumerated. It is, however, so crude an index as to be virtually only a qualitative measurement, and the only use we make of it to-day is in the negative sense, i.e., if it does not occur, in any given case, we suspect either that the patient is abnormally resistant or that the dosage he is receiving is too low.

(iii) **The Uric Acid: Creatinine Ratio.** Cortisone has a well-recognized uricosuric action. It probably acts by increasing the clearance through the renal glomeruli. It also has a definite but much smaller effect in increasing the excretion of creatinine. The constant rise in the ratio of these two substances in the urine was used as a relatively simple measure of the metabolic response to the drug It was soon discovered that whilst the initial response was constant, the subsequent results depended on many irrelevant factors such as the size of the "miscible pool" of uric acid, and it has been abandoned as a useful clinical test.

(iv) **Differential Analysis of the Plasma Proteins.** In rheumatoid arthritis there is a tendency for a reversal of the normal albumen : globulin ratio and a marked rise in the plasma fibrinogen. In the globulins, the greatest changes are in the alpha-I, the alpha-II and the gamma fractions Adequate suppressive therapy with cortisone always results in a tendency for these anomalies to revert to normal.

They do so at different speeds, and the alpha-II fraction in particular behaves very obstinately compared to the others. Chemical methods of estimating all these fractions are too laborious to be used as a routine, but it is possible to follow the relative changes very accurately by electrophoretic methods.

We have not yet applied these methods to sufficient cases to be sure of their clinical value It seems to be a line well worth following, particularly in relation to the alpha-II fraction, which, by virtue of its obstinacy, may be more specific than the others. There are biochemical methods which purport to measure this fraction alone, and at least one American worker has claimed that they are of considerable value in assessing disease activity.

Reverting to our original criteria for these tests, plasma protein studies are unlikely to help in case selection They could conceivably be of assistance in "screening" untried drugs, they are probably too inaccurate and cumbersome for routine use in solving problem[illegible] of dosage, but might well be of considerable help [illegible] of differentiating real from drug-ind[illegible]

Further investig[illegible]
and recent [illegible]
are currently [illegible]

(v) **Liver** [illegible] routine liver function tests are found to be [illegible] active rheumatoid arthritis The anomalies seem to be quite non-specific, and probably depend on the abnormalities of the serum globulins which have been discussed in the last section. These liver function tests do return to normal in most cases on

the steroid being administered. According to West and his group in Sheffield, this fixed proportion is constant for any one steroid but varies as between one steroid and another.

Based on this observation they have devised a method of assaying the potency of each of the steroid drugs by measuring the time it takes for

problems we have defined.

This is one of the few sections of this book where it is necessary to distinguish clearly between the cortisone group of drugs and corticotrophin

Corticotrophin acts entirely via the adrenal cortex, so that instead of atrophying and " going out of production ", the gland actually hypertrophies and produces considerably more hydrocortisone and allied steroids. These are represented in the urine by a marked increase in the excretion of both 17-ketosteroids and 17-ketogenic steroids.

Whereas excretion studies are of very little practical value in cortisone therapy they may be of considerable value in evaluating the adrenal responsiveness when using corticotrophin They are far too complex unfortunately for routine use, but in problem cases it is well worth while to estimate the output before treatment commences, and then to follow the changes in response to the " trophic " stimulation. Such records can also be of assistance at a later stage of therapy. For

different in either case

(ii) **Blood Steroids.** We have seen that the estimation of urinary steroids yields relatively little information of value to the clinician except in a few problem cases In addition the methods are laborious and involve the collection of twenty-four hour specimens of urine The difficulties of obtaining such specimens accurately from ordinary hospital wards (or, worse still, from out-patients) are notorious amongst all seasoned investigators In effect one needs either specially trained nursing staff or a separate metabolic ward to guarantee accuracy of collection

when they could be carried out routinely in an endocrine laboratory.

techniques which are currently available to us. Newer methods involving plasma steroid estimations and clearance studies may well bring to light detailed abnormalities which have so far escaped us Until they are discovered, however, it behoves us to avoid any facile assumptions, and to continue to approach the problem on the broadest possible front

(i) **Urinary studies.** The estimation of 17-ketosteroids has been standard laboratory practice for many years, and presented no serious problems in the study of cortisone and corticotrophin metabolism. Conversely it yielded very little useful information, since we were interested predominantly in those steroids which had a hydroxyl group and a ketol side-chain at the 17 position and less than 10 per cent. of these compounds are metabolized to, and excreted as, 17-ketosteroids.

Methods for measuring the total corticosteroids were available but they were extremely laborious and notoriously non-specific

To begin with, it was soon realized that they did not measure the significant quantity which was excreted in the form of conjugates. This led to a vogue for preliminary hydrolysis of the urine with an enzyme called beta-glycuronidase which was obtained from calves' spleens The effect of this was to make the estimation even more laborious without adding substantially to its accuracy or consistency. It was not until 1953 when Norymberski published his new method that a practicable technique of estimating the relevant steroids became available His method appears delightfully simple in essence It involves estimating the 17-ketosteroids by the standard method, then converting the corticosteroids to 17-ketosteroids by treating the urine with an oxidizing agent—sodium bismuthate, and the total 17-ketosteroids are then re-estimated The difference between these two estimations measures what are known as the 17-ketogenic steroids (17KGS) and represents that fraction which is derived from the corticosteroids *

The daily excretion of 17-ketosteroids and 17-ketogenic steroids of rheumatoid arthritics generally falls within the lower end of the range found in normal control subjects. If cortisone is administered there is initially a marked rise in the twenty-four hour output of both types This probably represents the proportion of the administered drug which has not been metabolized within the body. After about a week, there is a significant falling off in the daily excretion and this continues until a constant level is reached.

The cause of this falling off is undoubtedly the gradual decrease in endogenous production from the patient's own adrenal glands As with most endocrine secretions, the output of these glands is to a considerable extent regulated by the blood level of the corresponding hormone If this is artificially raised, as it is in cortisone therapy, then the endogenous secretion will fall off proportionately Eventually the adrenal gland may become totally functionless

At this stage the excretion products represent a fixed proportion of

* More recently, Norymberski has modified and improved his method The new step consists of a preliminary reduction of the steroid with sodium-borohydride Then all the ketosteroids formed by the subsequent oxidation with sodium-bismuthate must have come from the corticosteroids

induced suppression.

The details of this research have been published, but we feel that the results so far do not warrant the recommendation that these par-

orts will un-

ir estimating

3. Routine Procedures before Administering Cortisone

In the last two sections we have discussed—albeit inconclusively—the criteria by which patients are chosen for cortisone therapy. In this section we shall discuss the routine precautions which should be taken with those patients before treatment commences

We do not apologize that some of them may appear trite and self-evident; we have seen each of them neglected with dire consequences on occasion Our object is mainly to emphasize in general terms that the decision to start a patient on these drugs must never be taken precipitously or without obtaining certain basic data.

(i) **A full clinical history** must always be available with particular reference to the degree and duration of stiffness, the number of analgesic tablets required to control the pain in the course of twenty-four

mood swings, insomnia (not due to pain) and recent variations in weight.

(ii) **Full clinical examination.** In the course of this a careful record must be made of the blood-pressure, the immediate pre-treatment weight, the presence of hepatomegaly, splenomegaly, lymphadenopathy, œdema, acne or hypertrichosis. If these observations are neglected at this stage, sooner or later they are liable to be attributed falsely to the effect of the drug, which may even be unnecessarily curtailed on their account In the early days we always went to the

tenderness, pain on movement and range of movement. To chart the joints in this way at the start of treatment is certainly laborious, but the trouble taken is more than repaid by the ease of reference when assessing the progress of the patient on follow-up visits. In the absence of reliable

When this goal has been reached, a flood of information should become available on the clinical problems of cortisone therapy.

For example it seems logical to hope that such knowledge will overcome the difficulties of gauging dosage requirements of these drugs and will enable us to assess the extent to which variations in clinical response correlate with variations in the levels of circulating steroids.

These problems have been discussed at some length because of their fundamental importance in understanding much of the current research on the subject. Unfortunately they have little *immediate* application to our main problem of providing laboratory indices for the clinician.

D. Acute Phase Reactions

We have until now confined our discussion of laboratory tests to the orthodox, the logical or the near specific. We now enter a realm characterized by empiricism and complete lack of specificity. Nevertheless it is one of considerable interest, and since empiricism and practical usefulness are by no means mutually exclusive in medicine, it is quite possible that the solution to our problems will eventually be found within this group

The term "Acute phase reactions" was coined by the Americans to classify a large group of serological reactions which become abnormal during the acute phase of any generalized inflammatory process. The best analogy from the orthodox field is the erythrocyte sedimentation rate.

Although equally non-specific, these newer tests depend on many and little understood factors Indeed they do not always run parallel with each other, although their trends are usually in the same direction.

Because most of them have emanated from empirical and unrelated observations they are remarkably diverse in type and correspondingly difficult to classify. A few of them will therefore be listed in a random order

- i The Serum "C reactive" protein,
- ii. The Serum "Winzler" mucoprotein,
- iii. The Serum Hexosamine,
- iv. The Serum Total Polysaccharides,
- v. The Serum Diphenylamine reaction,
- vi The Serum Viscosity,
- vii. The Serum Anti-hyaluronidase titre,
- viii The Serum Complement,
- ix. The Plasma Amino-tripeptidase level

All these indices tend to be raised in active rheumatoid arthritis, and the author has recently applied a selection of them to a group of cortisone-treated patients with the object of investigating how much help they can give in solving our clinical problems. All except one of these tests are relatively simple and rapid to perform and could be used in routine clinics if they proved helpful

The results of this investigation were unfortunately inconclusive. Most of the tests were more consistent and reliable than the erythrocyte sedimentation rate, but none of them was sufficiently sensitive or

serum hexosamine, by virtue of the obstinacy of their response to cortisone, are useful in differentiating true remissions from cortisone-induced suppression.

The details of this research have been published, but we feel that *the results so far do not warrant the recommendation that these par-*

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laboratory tests, in fact, it will be found to be the *only* practicable way of making this assessment. The patient's memory and subjective assessment is usually totally unreliable within about a month from the commencement of treatment.

(iv) *A functional chart of the patient's status before treatment, corresponding to the joint chart*, is extremely useful to have. This is carried out by a selection of simple functional tests, examples of which, together

test of the urine for glycosuria is obligatory.

Optional precautionary investigations include an electrocardiogram and a measurement of the serum electrolytes. These are occasionally useful when investigating complications If osteoporosis is suspected, it is advisable to obtain standardized x-rays of a selection of bones These can be compared photometrically with later films taken with a similar technique If the porosis is measurably increased, it is a strong warning sign to reduce or cease the treatment In practice, these

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It is first of all very important to make it quite clear that we are embarking on a treatment of the disease and our primary object,

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which is visible above the water-line will vary a little from day to day but this does not mean that the total mass of the berg is altering.

The entire iceberg corresponds with the total activity of the disease, the suppressed symptoms of the disease correspond to the submerged part. The remaining one-eighth represents the residual symptoms which the patient *must learn to tolerate In most cases it is neither* practicable nor desirable to render the patient completely symptom-free It usually means that the dosage is unnecessarily high and it certainly tends to lead to abuse of their joints by all but the most *cautious of patients*

The last point is very important, and patients must be instructed that whilst our aim is to make them comfortable and useful citizens, excessive physical exertions on their part will militate strongly against the success of the treatment In the first place it will almost certainly increase the dosage requirements. In the second place we know that cartilage and bone destruction can continue even under efficient cortisone suppression and that *this process is greatly accelerated by trauma* or overuse

Next, we always warn our patients about the inevitable cosmetic

effects associated with prolonged therapy A lady who has accepted the inevitability of facial " mooning " and a mild degree of hypertrichosis as the price to be paid for the relief of her pain, is a far easier person to handle than the same lady whose initial flood of enthusiasm for the treatment is succeeded by these blows to her vanity a few weeks later. By this time, to increase her anger, she will probably have forgotten the severity of the symptoms from which she has been delivered

We warn our patients explicitly of the risks involved in the too-sudden withdrawal of the drug We instruct them always to call in their doctor in the event of intercurrent illness, and tell them that since cortisone may suppress the severity of the symptoms, it is better to be cautious and to obtain advice rather earlier than they would normally do We explain to them that in the event of their having to have an operation or undergo significant stress, they must always make sure that their doctor knows that they are—or have been—on cortisone therapy so that he may take the appropriate precautions.

We also make it clear to them that they are not required to stop taking their customary analgesic drugs just because they are on corti- [illegible]

that we may use it as a crude index of their progress

[illegible]

maintenance of the joints in their optimal positions become more important rather than less as their function improves Cortisone must never be used as a prop by the arthritic to excuse him from those disciplines which are so vital to his successful survival in society

If the patient is to be maintained on corticotrophin rather than cortisone, we endeavour to instruct him, or a close relative, how to inject it We also make sure they know how to distinguish the different types of preparation and note that it is marketed in two or three different potencies Therefore they should always check the labels on each new bottle before administering it

We then encourage the patients to voice any of their own doubts or worries about their new therapeutic venture It is surprising to learn just how much anxiety can be concealed beneath their apparently bland acceptance of all that we have told them. Much of this is based on " scare " stories culled either from the sensational medical articles in the lay press or from their fellow patients who seem to take the greatest delight in spreading alarm and despondency, based usually on third-hand information

[illegible]

Finally we re-stress the fact that the treatment we are about to institute may need to be carried on in perpetuity, and that its chances of success are strictly related to the risk of complications. A great many

laboratory tests, in fact, it will be found to be the *only* practicable way of making this assessment. The patient's memory and subjective assessment is usually totally unreliable within about a month from the commencement of treatment.

(iv) A functional chart of the patient's status before treatment, corresponding to the joint chart, is extremely useful to have. This is carried out by a selection of simple functional tests, examples of which, together

test of the urine for glycosuria is obligatory.

Optional precautionary investigations include an electrocardiogram and a measurement of the serum electrolytes. These are occasionally useful when investigating complications. If osteoporosis is suspected, it is advisable to obtain standardized x-rays of a selection of bones. These can be compared photometrically with later films taken with a similar technique. If the porosis is measurably increased, it is a strong warning sign to reduce or cease the treatment. In practice, these refinements are seldom employed in this country.

(vi) "Briefing" the patient. We have already said, that as far as possible we limit the use of cortisone to those patients who have the

some of the avoidable risks

It is first of all very important to make it quite clear that we are embarking on a *treatment* of the disease and our primary object, unfortunately, is *not* to effect a *cure*.

In order to illustrate this point, we sometimes make use of Hench's metaphore of the iceberg which may be seven-eighths submerged, but the invisible part is as potentially serious as the visible The amount which is visible above the water-line will vary a little from day to day but this does not mean that the total mass of the berg is altering.

The entire iceberg corresponds with the total activity of the disease, the suppressed symptoms of the disease correspond to the submerged part The remaining one-eighth represents the residual symptoms which the patient must learn to tolerate In most cases it is neither practicable nor desirable to render the patient completely symptom-free It usually means that the dosage is unnecessarily high and it certainly tends to lead to abuse of their joints by all but the most cautious of patients

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At the same time, there will be a marked increase in the active and passive range of movement in all those joints previously limited by spasm and pain.

(iv) At this stage the patient often exhibits some degree of euphoria; he may become quite uncritical in his enthusiasm. He may find it extremely difficult to concentrate as new thoughts and ideas crowd in upon him This naturally may lead to insomnia in some cases. The psychic state can range from a pleasant degree of mental alertness such as can be produced by the amphetamine group of drugs, to the condition called " hypomania ". The physician must be alert to the potential risks of a fully developed phychosis and must be prepared to cut the dosage and give sedatives which are appropriate to his evaluation of the condition.

(v) Another semi-objective phenomenon which *may* be related to

a new optimum is reached. It is difficult to be sure to what extent

sion is used to describe the characteristic last-minute flop when the arthritic lowers himself as gently as he can into a low chair. It is remarkable how quickly patients regain their ability to control

All these objective responses to therapy will occur slightly more rapidly with corticotrophin than with oral cortisone Intramuscular cortisone acts slightly more slowly than either of them.

5. Routine Procedures to be carried out at Follow-up Clinics

Before describing these in detail, two fundamental questions must be discussed: namely, the frequency at which these patients should be checked in a cortisone clinic and the desirability, or otherwise, of taking patients into hospital for the initial phases of the treatment.

These questions are to some extent interrelated, the second and more controversial one may be answered by stating that it is preferable, but

of these can be anticipated and reversed if they are recognized at an early stage. This early recognition must depend on the patient's own

ing cortisone administration may place a great strain on his wasted and toneless muscles. This may lead to severe pains of *mechanical* origin.

It is our habit nowadays to delay the start of cortisone therapy in such a patient until he has had a course of the appropriate physiotherapy. In the case of the feet we order routinely a course of faradic foot baths and active exercises of the intrinsic and extrinsic muscles.

4. The Pattern of Response to Cortisone

" average " patient who is receiving an adequate suppressive oral dose from the beginning.

morning this loss of early morning stiffness will be a very marked feature. It will be reflected objectively in his ability to get out of bed as soon as he awakens and to perform his ablutions and get dressed. This freedom contrasts markedly with the slow and painful process of mobilization which characterizes most rheumatoid arthritics in the active phase.

The objective changes which may be expected to occur within the next few days consist of:

(i) A measurable diminution of joint swelling and a corresponding diminution in the size of the joint effusions.

(ii)
ments
have o

not blind us from recognizing it and measuring it to the best of our ability.

(iii) The tenderness of the joints to pressure and their increased heat usually disappears surprisingly rapidly until they can tolerate considerable pressure.

We are alert for other stigmata such as acne vulgaris, "striæ distensæ", hypertrichosis, or pathological bruising. We pay special attention to the patient's mood, noting any unusual emotional lability, euphoria or garrulity.

(iv) With regard to the examination of the musculo-skeletal system itself, we select the six worst joints in the body for detailed assessment on each visit. We also record whether any new joints have become involved or old ones cleared up since the patient was last seen. The size of any nodules or bursæ is noted, also the condition

speed, power, co-ordination and mobility. Where possible the movements involved should bear some relation to those which the patient will be required to make in his daily life. In addition it is

structural changes

As a special test we invariably include a grip test when any of the finger joints or the wrists are involved The simplest method of carry-

recorded and it is surprising how constant the results are once the patient has had a little

cury at least to the top

sidered to be normal

the same cuff folded in the identical way on each occasion. If it is unfurled on each occasion a small error is bound to creep in This may be quite insignificant for ordinary requirements but should be avoided if the records are going to be used for clinical research.

Another useful objective test, which we use when there is time, is to measure the swelling of the proximal inter-phalangeal joints with jeweller's fitting rings. These can be obtained quite cheaply and it is interesting to confirm one's fallible clinical impressions with objective evidence of this nature

This entire clinical check-up takes about fifteen minutes when a routine has been established We appreciate that it would not always be practicable to spend so long on each patient in a busy clinic We nevertheless maintain that the more documentary evidence of this sort which the clinician has at his disposal, the easier will become his task of controlling patients who are on long-term cortisone therapy.

A specimen record sheet which we use for this purpose will be found in the Appendix

by no means essential, for cortisone therapy to be commenced under hospital supervision. Ideally we believe that such patients should remain as in-patients for about two weeks during which their metabolic, psychological and arthritic response should be kept under very close scrutiny. A shrewd guess can generally be made at the end of this time as to whether they are going to be good or poor responders and one can even predict to some extent the type of side effects—if any—they are most likely to develop.

A small practical point arises here on the problem of the maintenance dosage. Often it is advisable to send patients home on a dose about fifteen per cent. higher than the level required under hospital conditions Frequently the dose requirement rises slightly as they resume the stresses of home life and the patients become despondent if they get an increase in symptoms as soon as they arrive home. Usually this increased dose can be lowered very quickly, but it is always wise to anticipate the problem and warn the patients explicitly about it.

The problem of how frequently they should be followed up certainly cannot be answered by rule of thumb Until their maintenance dose is finally established, and certainly for the first four or five weeks, we recommend that they attend weekly After the dose has been worked out the necessity for follow-up visits depends on many factors, of which the most important is the level of the dose itself

For example a patient who can be maintained comfortably on 50 mg. or less a day is running virtually no risk at all and can be seen at an interval of several weeks By contrast, a patient who requires around 100 mg. of cortisone per day for maintenance, should be checked at three-weekly intervals at least until it is absolutely certain that he is tolerating the drug well

It has been found that 75 mg cortisone per day represents the critical level above which the incidence of complications rises steeply.

Other factors which would naturally influence the frequency of follow-up are the distance the patient would have to travel, his intelligence, and ability to test his own urine and to recognize warning [illegible]

therapy Only on very rare occasions do we risk leaving the patients unsupervised for longer periods than this, unless they are on very low dosages.

On the occasion of each visit to the follow-up clinic, we recommend the following procedures.

(i) The patient is asked about his subjective response in general, [illegible] ppetite [illegible] about [illegible] nusual [illegible] tr [illegible] lly the [illegible] sits of fat, the presence or absence of œdema, and the blood-pressure

We are alert for other stigmata such as acne vulgaris, "striæ distensæ", hypertrichosis, or pathological bruising We pay special attention to the patient's mood, noting any unusual emotional lability, euphoria or garrulity.

(iv) With regard to the examination of the musculo-skeletal system itself, we select the six worst joints in the body for detailed assessment on each visit We also record whether any new joints have become involved or old ones cleared up since the patient was last seen The size of any nodules or bursæ is noted, also the condition of the wasted muscles and the development of any new deformities

Finally, we record the results of four or five simple tests of function (see Appendix) These are specifically selected for each patient The basis for the selection is that between them they should test speed, power, co-ordination and mobility. Where possible the movements involved should bear some relation to those which the patient will be required to make in his daily life In addition it is

structural changes

As a special test we invariably include a grip test when any of the

easily be gripped in the palm of the hand It is then attached to the machine and the mercury blown up until it registers 30 mm The patient is then asked to exert his maximum grip, hold it for about three seconds and then release it The average of three readings is recorded and it is surprising how constant the results are once the patient has had a little practice An adult can usually push the mercury at least to the top of the tube, and anything above this is considered to be normal For additional accuracy, it is advisable to use the same cuff folded in the identical way on each occasion If it is unfurled on each occasion a small error is bound to creep in This

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6. Restrictions to be placed on the Patient receiving Cortisone

In very many cases, there is no need to restrict the patient's way of life at all. As already mentioned, he should be warned to avoid, as far as possible, any excessive physical or mental exertions. If it is at all possible he should try to rest for a short period each afternoon on his bed. Dietetic restrictions are relevant in comparatively few cases. Thus, if one decides to give the drug to an arthritic who is already obese, it is essential to instruct him in the principles of the low-calorie diet. In fact if there is no particular urgency, we prefer to get him started on weight reduction before the treatment commences

When a patient starts to put on weight rapidly under the influence of cortisone, our first concern is to decide whether this is mainly the result of sodium retention. If it is not, we have to use our discretion before deciding whether any restrictions are necessary No rigid rule can be laid down but, in general, if the increase exceeds four or five pounds a week it is probably excessive However if the patient was severely cachectic before treatment we consider it to be meddlesome and illogical to restrict his intake until he has reached his average pre-illness weight Once he has regained this we believe it to be legitimate to advise mild or severe dietary precautions according to the speed at which he is gaining weight.

If the weight gain is associated with a significant degree of sodium retention, there will probably be ankle or sacral œdema to give a clue as to its ætiology If the patient is in hospital, the fluid-balance chart will give an important indication of what is happening, whereas in the case of an out-patient one has to rely on the patient's own observations about his fluid output.

Restriction of the sodium intake in these circumstances becomes of paramount importance, and this can range from a mild régime which allows no salt to be added to the food, to the strictest type of régime which necessitates the use of special salt-free bread and butter in an effort to reduce the sodium chloride intake to less than one gramme per day.

Since sodium retention is automatically tied to some extent to potassium diuresis in these cases it represents one of the strong indications for giving added potassium. This can be done by administering about five grammes of potassium chloride (or nitrate) in enteric-coated capsules daily. It is often convenient to give at least part of this in the form of a potassium chloride salt substitute.

Potassium in these circumstances, frequently has a diuretic effect on its own, but where this does not occur, it is perfectly legitimate to use any of the orthodox diuretic drugs such as Mersalyl or Diamox. There are some who advocate the use of ion-exchange resins in order to combat this complication, but from our limited experience of them they seem complicated to prescribe and extremely unpleasant for the patient to take, consequently we very seldom employ them

The dietary recommendations of one American group may be summarized as follows:

(a) Adequate calories.
(b) High proteins (between 120–200 g of good-quality proteins

psychoses, muscle weakness and insulin resistance (where diabetes has been produced).

(*e*) High fat, which was found to reduce 17-ketosteroid excretion and some of the cosmetic manifestations resembling those of Cushing's disease.

7. Radiographic Help in Cortisone Therapy

affected joints.

Apart from the arthritic changes, we pay special attention to the texture of the bones for, as has already been stressed, osteoporosis is a relative contra-indication to the use of these drugs. If it exists, it is extremely important to watch it carefully on standardized films to ensure that it is not increasing

gressive erosions during continuous and adequate cortisone suppression.

tainly learned that it was both useless and unnecessary to restrict their

activities It therefore seems quite illogical to over-stress the seriousness of a drug-induced condition which seems to be identical.

8. Dosage Schedules

We mentioned in an earlier chapter that there have been very significant developments in our views on this subject since 1949. In those days it was the habit to initiate
For example, we used to give routine
mg. for the next three or four days, th
response appeared to be optimal (or
reduced to a maintenance level

This schedule gave rise to the extremely dramatic results which were

to become so excited that he often became very difficult to manage. The excitement was partly drug-induced and partly the natural response of a long-term invalid on whom an apparent miracle had been wrought. No matter what the cause, the result was undesirable, not only because of its immediate manifestations, but because it set a standard of well being which it was both impracticable and dangerous to maintain for a long period A patient who has thus "flirted with paradise" did not take kindly to the inevitable return of his symptoms as the dose was reduced. Such patients, having set their standards too high, frequently became querulous and disgruntled Of those who did not merit this description, many seemed to lack the enthusiasm and desire to co-operate when it was explained to them that they were expected to tolerate some degree of discomfort permanently, for the sake of safety.

As soon as these serious disadvantages were appreciated, there came a flood of modified schedules, each one claiming special advantages over the one it supplanted Hench has included eleven examples of these in a chart he published on the subject in 1954 It is unnecessary to describe them in detail as, in effect, they were all variants of four basic themes, namely the "high-low", the "low-high", the "constant", and the "intermittent" In addition there were a few complex régimes which recommended alternating cortisone and corticotrophin. These were designed to avoid the atrophy of the suprarenals which is an implicit risk in long-term, uninterrupted cortisone therapy

The *intermittent* type of schedule is definitely obsolete since it was found to be unpleasant and probably harmful to the patient to produce violent swings in symptoms In addition it represented a series of most unphysiological insults to the suprarenal glands As soon as oral therapy became available the rapidity of the relapse at the end of each course removed any justification for this type of therapy

Each of the other schedules still has its advocates, and possibly some special applications which we will try to define·

High-low schedules are indicated, in our opinion, in very acute disease where time is a very important factor This is a situation which is quite commonly encountered when treating such diseases as acute

rheumatic fever or acute disseminated lupus erythematosus It is, however, relatively uncommon in rheumatoid arthritis for the disease to be so fulminating that time is such a vital factor Its disadvantages have already been discussed. Where it is administered for life-saving reasons, these objections must be overruled and each case judged on its merits

Low-high schedules are tedious to apply and it is sometimes very difficult to arrive at the ideal maintenance dose. We think that they are only indicated when we are doubtful about the advisability of giving

common. We have already stressed that there is no tissue sensitivity test available and that we have to rely on trial-and-error methods In these circumstances it is plainly desirable to start on the lowest possible dose and gradually to increase it until we arrive at the maximum which is considered to be compatible with safety

If the patient has not shown a reasonable response by this stage we can safely withdraw the drug without risking significant psychological or endocrinological trauma Occasionally we achieve a surprisingly gratifying result by this method On principle we are opposed to using cortisone merely for its analgesic effect, but it does seem justifiable to do so if a patient can be made happier on a dose which is very unlikely to cause serious complications. For this purpose it is usual to commence

latter in most cases since it enables the physician to observe the optimum response within a reasonable time If the response is not satisfactory at this level, he will be able to make an early decision to suspend treatment, because it is almost never justifiable to maintain a rheumatoid arthritic for more than a few days on a dose which exceeds 100 mg. per day

If the initial dosage is 75 mg there is an inevitable delay of up to a month while the higher doses are being tried By this time the patient may have become used to the drugs which will make it difficult to suspend treatment

As soon as a satisfactory response has been achieved it is time to start cutting the dose very gradually We can define "satisfactory response" for this purpose as a state of *reasonable* comfort with no acute pain and minimal morning stiffness Functionally the patient should be independent as regards normal activities of daily life, and should be able to undertake at least part-time work, or in the case of a woman, to be able to do light housework We do not seek to make the patient pain-free before reducing the dose The reduction should never exceed 12½ mg. at a time, and each stage should be maintained for at least two or three days. If, as commonly occurs, the patient suffers a

symptomatic flare each time the dose is reduced, the new level should be maintained until that flare has settled. Although we have not yet had much experience with smaller decrements than this, we believe that there may be an advantage in using 5 mg tablets for this purpose, and these are now available in this country.

Eventually, by this means, a satisfactory maintenance dose will be found It may be necessary in some cases to go below this dose and then raise it. This is because of the crude methods of evaluation which are available to us. It is highly undesirable, because occasionally when a patient escapes from control it may be a tedious business to bring him under control again Indeed, it may involve a return to considerably higher doses and a second period of close observation. Fortunately this problem does not occur very frequently.

The average maintenance dose in at lease three independent series has been recorded at 69½ mg. per day, and the individual range is from 25 to 100 mg per day.

9. "Tailoring the Dose"

We have used this expression elsewhere in this book and now it behoves us to explain what Hench had in mind when he introduced it into his writings.

When the drug is taken by mouth, it is rapidly absorbed and then rapidly metabolized and excreted The effective duration of action is from one to six hours after ingestion with a peak round about three hours.

The object of the treatment is to keep the patient's symptoms suppressed for the greater part of each day. Now it is well recognized that the severity of rheumatoid symptoms varies considerably in the course of the twenty-four hours In any individual patient they tend to follow a set pattern, and whilst the majority seem to be worst when they awaken in the morning, this is by no means a constant feature. Hench argues that the size and spacing of the doses should be planned on the basis of these cyclical variations, and that each patient must be studied as a separate problem To give an inadequate dose to cover the worst period of the day or a dose which is more than adequate for a good period is illogical, as the incidence of side-effects seems to be related to the total intake daily no matter how it is divided up

By applying this concept of "dose tailoring" intelligently instead of slavishly following the orthodox "t i d" type of prescription, it is sometimes possible to effect a saving of up to 25 per cent. of the daily dosage without the patient suffering a perceptible increase in his discomfort. This principle should be applied whenever the dose has to be reduced.

Quite apart from considerations of logic, it is surprising how much more co-operative the patient will become when his help is elicited in this way in the planning of his therapy. We consider that oral cortisone should never be prescribed less than four times a day. To give it only twice per day as is sometimes done, is grossly wasteful, and although twice-daily doses may seem satisfactory in the high dose range it

becomes more difficult to keep a patient comfortable throughout the day when he is on low dosage.

The second type of individual planning on which Hench insists, concerns the day-to-day variations in requirements. Most rheumatoid arthritics fluctuate in the severity of their symptoms from day to day. These fluctuations in any one period may be relatively mild, and hitherto they have been largely ignored by clinicians in favour of a more comprehensive evaluation over the whole period.

However obscure they are to the onlooker, these fluctuations are very real to the patient, and he is the only person who can assess them, since they are largely subjective in nature.

[illegible]

(e.g. week-ends). On other days, either because the symptoms are more severe than usual, or because the patient knows that he has a [illegible]

placed on such a régime. It naturally involves discrimination by the clinician before he selects which patients are intelligent enough to co-operate, and we always insist that they keep a careful record of their daily intake, at least for the first month or two.

10. Relative Dosages of the Steroid Drugs

Throughout this book so far we have used the words "Cortisone Therapy" synonymously with "Steroid Therapy" except when we were discussing specific properties of corticotrophin. In this section, however, when dosage schedules are being discussed, it is plainly [illegible] their explanation.

[illegible]

or the speed at which it is released from its vehicle in the case of long [illegible]

the suprarenal cortices of hypophysectomized guinea-pigs of their ascorbic acid content. The standard against which they are all

TABLE I
EQUIVALENT DOSES OF STEROID DRUGS

Cortisone mg day	Hydrocortisone	Delta-Cortisone (Prednisone)	Delta-Hydrocortisone (Prednisolone)	Soluble Corticotrophin (administered 4 times a day)	Corticotrophin Gel (administered once a day)	Corticotrophin (administered in a drip transfusion over 8 hours)
100 mg	70–80 mg	20–25 mg	20–25 mg	60 units	40 units[1]	5 units

[1] This figure is based on experience and conflicts slightly with the claims of some of the manufacturers

TABLE II
RELATIVE COSTS OF STEROID THERAPY

Cortisone mg /day	Hydrocortisone (free Alcohol)	Delta-Cortisone (Prednisone)	Delta-Hydrocortisone (Prednisolone)	Corticotrophin
100	80	25	25	20 units
3s 6d	4s 2½d	4s 7d	4s 7d	No price available.

100 mg hydrocortisone acetate for intra-articular injection 8s 4d (Hydrocortisone TBA approx. double the price)
Relative cost of skin ointment, 5G tubes 1% 5s 3d 2½% 12s 0d
Hospital prices, July 1957

compared is one of the original preparations manufactured by Armours

With these few words of explanation we can proceed to construct a comparative dosage table. (See page 68)

11. Which Steroid to Use?

The increasing range of steroid drugs which is becoming available for use year by year makes this question both relevant and topical We have not yet had enough personal experience in this country to give a firm opinion about all the newer products, we can however discuss some of the principles by which we will approach this subject.

(i) **Cortisone versus Corticotrophin.** As soon as it was discovered that cortisone was almost as effective by mouth as by injection, there was naturally a rapid swing in its popularity as compared to corticotrophin which, in those days, had to be injected at least four times a day This, and its slightly lower price, is probably responsible for the fact that almost all the long-term clinical studies which have been published have been about cortisone rather than corticotrophin

Within the last eighteen months, however, the results of two controlled clinical trials have been published Their startling conclusions

[illegible]

already known that in a small proportion of cases there may be an individual idiosyncrasy causing a poor response to one but a good one to the other

To explain how a patient can be resistant to cortisone and sensitive to corticotrophin we could hypothesize that they lack the necessary

[illegible]

applications

Another advantage which is claimed for corticotrophin over cortisone is that since the suprarenal cortices hypertrophy rather than atrophy with this drug, it should give rise to a less severe "rebound phenomenon" when it is withdrawn. Our experience does not accord with this theory, and indeed, a little more thought will show it to be invalid

Whilst it is true that the suprarenals hypertrophy with corticotrophin

it is equally true that the anterior pituitaries of these patients become atrophic. Under the microscope they show a characteristic hyaline change as described by Crookes.

It is hardly surprising that this should be so because the function of the pituitary, like most other endocrine glands, is governed automatically by the circulating level of the hormones for which it is responsible. In the case of a gland like the pituitary, which secretes so many different hormones, it seems that this "servo" effect is very specific and that each hormone will affect only its appropriate "trophic" secretion from the pituitary

The disadvantages of corticotrophin over cortisone have been discussed elsewhere They include the necessity for administering it by injection; the fact that a state of true resistance may develop after a time, and the fact that it is significantly more expensive than cortisone. As a compromise some authorities recommend that corticotrophin should be given on about three or four days a month to any patient who is on long-term cortisone therapy. It is claimed that by doing this, one combines the advantages of both drugs and minimizes their disadvantages. We have no personal experience of this régime.

(ii) Cortisone versus Hydrocortisone, Prednisone or Prednisolone. Here again, relative costs will play a major part in deciding which drug to select. At present cortisone still remains the cheapest drug to administer However prices must depend to some extent on public demand and the possibility of mass production Because of this it is quite probable that the newer drugs may eventually become cheaper than the parent substance to synthesize Until this occurs, however, cortisone will probably remain the drug of choice for all routine cases in spite of the fact that the others appear to possess significant advantages over it.

Hydrocortisone was formerly reserved for patients who exhibited primary resistance to cortisone or whose toxic : therapeutic ratio was so narrow that treatment was constantly prejudiced by the risk of serious side-effects It is about twenty or thirty per cent. more potent, and this does not appear to be associated with a corresponding increase in toxicity in most cases As a result the gap between the maintenance and the toxic dose may be widened just sufficiently to allow therapy to continue in cases where it would otherwise have had to be withdrawn.

It is probable that the advent of prednisone and prednisolone will oust systemic hydrocortisone from practical therapeutics, but it is too early to be sure of this yet. These new drugs are about four times as powerful as cortisone on a weight-for-weight basis. Their action also appears to start far more rapidly and the "rebound" relapse when they are left off is also more intense.

From the articles which have so far been published, and from our limited experience, it seems that they will accomplish all the therapeutic effects of cortisone. The incidence of most of the side-effects appears about the same, except that there are disturbing reports demonstrating that there is a higher incidence of peptic ulceration and possibly also of psychoses. The great advantage claimed for these drugs, apart from

their remarkable potency, is the negligible effect which they have upon

to switch a patient from cortisone to prednisone if any of these complications develops in the course of therapy to an extent which might jeopardize its continuance. The presence of dyspepsia would be a relative contra-indication to the switch We have not enough evidence to state definitely whether facial mooning and other cosmetic side-effects can be diminished by the use of prednisone Our impression so far is that they are about the same as with cortisone.

Another legitimate reason to switch a patient from cortisone on to prednisone would be the development of resistance to the former. In a recent trial fourteen such patients were switched without their knowledge Ten of them improved considerably, both subjectively and objectively; four of them noted no important difference, but the significant thing is that none of the fourteen, when asked, preferred the cortisone to the prednisone.

According to present information there is no detectable difference between the clinical results obtained with prednisone or prednisolone. The dosage and the results appear to be identical

There are some who advocate the routine use of alkalies and other prophylactic measures against peptic ulceration in every patient

that this is a practice which is not to be recommended, because it adds to the cost and confusion of steroid therapy.

12. Deterioration on Long Term Treatment

jective flare, which is so commonly seen in these patients?

If one decides that it is a genuine relapse, the next points for con-

, a

phenomenon discussed at length elsewhere.

The distinction between these four possibilities can be extremely difficult and sometimes impossible. Nevertheless, although we can [illegible]

the problem arises. At the moment we confess that our verdict must often depend to some extent on an inspired guess

The logical counter measures which are indicated would be different in each case. For example, a temporary and largely subjective flare can either be ignored or can be covered with an extra supply of analgesic drugs until it has settled. We have discussed earlier the method of "tailoring the dose" which can sometimes help to meet this contingency

If the flare appears to be due to the gradual development of drug [illegible]

adaptation" to drugs in rheumatoid disease. We are, however, convinced that it is a frequent and real occurrence and that it is not peculiar to the steroid group of drugs It explains why it is usually the first course of gold which does the patient most good, subsequent courses often being very disappointing. The same tendency is frequently seen in patients who respond dramatically to phenylbutazone in the early stages of its administration

If there is evidence that the deterioration is due to a true flare and spread of the disease, the logical counter-measure is to increase the dose of cortisone to the limits of safety in an effort to suppress it. Any adjuvant measures such as large doses of aspirin or even of phenylbutazone are legitimate if the flare defies the raised cortisone dosage. It would again be reasonable in these circumstances to change to one of the more powerful steroids if one is forced above the safety level with cortisone.

There are occasions when one has to break one's own rule that the maintenance dose of cortisone should never be above 100 mg /day, in order to deal with these contingencies. We have occasionally arrived at very large daily dosages in these circumstances without apparently [illegible] It constitutes one of the relative emer- [illegible]

[illegible] at "hypercortisonism" when it is diagnosed has been discussed fully in an earlier chapter and will not be repeated here

13. When and How to Withdraw Cortisone Therapy

There are three common reasons why one may wish to discontinue cortisone They are, in approximate order of frequency:

(i) Because of an unsatisfactory response
(ii) Because of side-effects which are either dangerous or intolerable to the patient.
(iii) Because one suspects that the patient may have gone into a relative or complete remission and no longer requires the drug

(i) Unsatisfactory response. This may be either "primary" or "secondary" By a "primary" poor response we mean that the patient has never derived significant benefit from therapy from the commencement. It may be that he is, *a priori*, an unsuitable case who should never have been selected, or he may show an unpredictable degree of cortisone resistance A more common situation is where a physician is driven in desperation—all else having failed to provide relief—to carry out a therapeutic trial with steroids. He may hope that although the patient does not fulfil many of our criteria for long-term cortisone treatment he will prove to be unusually sensitive and derive some comfort from low and safe doses of the drug

We have confessed that our criteria are relative and not absolute, and that we frequently obtain both pleasant and unpleasant surprises even when we adhere strictly to them We must therefore not be inconsistent and decry such empirical trials even though the majority are doomed to disappointment. We do insist, however, that the physician must have a clear conception of what he is doing from the beginning He must not use cortisone and [illegible]

cases and be prepared to admit defeat before the dosage ever reaches the toxicity range In the case of cortisone, we would consider any- [illegible]
more difficult as the trial is extended beyond this period

By a "secondary" poor response we are referring to the patient whose initial response was satisfactory, but who gradually seems to derive less and less benefit for reasons such as those discussed in the last section If all the counter-measures mentioned there prove unsatisfactory, one should decide to cut one's losses and discontinue treatment either temporarily or permanently

(ii) Side-effects. These can be arbitrarily divided into two groups The first of these consists of complications which may seriously endanger the patient's well being, such as severe osteoporosis or uncontrollable dyspepsia The second group consists of those which are unpleasant and distasteful to the patient but do not incur the risk of permanently impairing his health Inevitably there is a hinterland between these broad groups (e g steroid diabetes) where the complication is certainly serious but where there is room for controversy about the advisability of continuing treatment

Ignoring the second group for the moment, one can dogmatize by

saying that the threat of a dangerous complication leaves no alternative but to stop treatment as soon as possible.

In the non-dangerous group, the clinician's discretion must be influenced by the patient's own susceptibilities. Indeed the patient will [illegible]

naturally vary enormously according to such diverse factors as age, personal vanity, social status and occupational commitments, not to mention the severity of the disease.

We strongly recommend that in each case the physician takes the patient entirely into his confidence, tries to weigh up the indications and contra-indications for continuing treatment as accurately as he can, and then gives the patient an opportunity to consider them in his [illegible]

true remissions from cortisone suppression has already been discussed in another section. It can be a very difficult question, whose solution may finally depend on a trial withdrawal of the drug. The decision is even more difficult when one is dealing with *partial* remissions versus *partial* suppression, because here a quantitative as well as a qualitative assessment creeps in.

A further difficulty is that the symptoms which may result from each reduction of the dose have to be differentiated into those which represent the tissues' temporary protest against any reduction in the level of circulating hormones to which they have become accustomed, and those which represent the true recrudescence of underlying arthritis To some extent the same differential points hold good as in the diagnosis of "hypercortisonism", but in the present problem one can invoke the aid of time, for natural withdrawal symptoms will always tend to settle down within a few days, whereas the reverse may be expected to occur in a true flare of the disease

With regard to the second part of our problem, namely how to withdraw cortisone, there is very little to be said that is not either common sense or common knowledge. The withdrawal must be carried out slowly and patiently. We can think of no emergency which justifies [illegible] ble speed of [illegible] l largely by [illegible] ral rule we [illegible] time, and a [illegible] wo days. [illegible] th the dose [illegible] authorities [illegible] should be [illegible]

since once the cortisone has been completely withdrawn, the process has to be started all over again with corticotrophin, and this can sometimes be almost as troublesome

14. Is Short-Term Steroid Therapy ever Justifiable?

The majority opinion on this question to-day would be a resounding and confident "No", except in one or two very special circumstances which will be discussed presently. We believe, however, that there

to the patients. We believe that in a proportion of cases it can do positive physical harm in that the rebound phenomenon may last a very long time, and some patients appear to deteriorate permanently from such an experience.

is particularly reprehensible when it is done to cover a short hospital admission, so that the patient is discharged, so to speak, on the "crest of the wave," leaving his harassed general practitioner to deal

sionally the remission lasts two or more years. We are convinced from experience that these results do not justify the misery and damage

cases, and one claims that this occurred in 24 per cent., which is quite

exceptional. It is not clear whether this series included all the cases who claimed subjective relief or if it was confined strictly to objective criteria

Writing in 1954, Hench gives the following six indications for short-term therapy

(i) Episodic rheumatoid arthritis;
(ii) Patients who are relatively intolerant of the drug in usual doses;
(iii) Patients who need dangerously high doses to control their symptoms;
(iv) Those patients who have relative contra-indications to the use of these drugs, such as peptic ulcer, diabetes or nephritis;
(v) To assist or supplement short intensive courses of physical therapy or orthopædic procedures,
(vi) Patients who are anxious about the prospects of long-term treatment

Of these we would only be prepared to agree to the first and the fifth unequivocally The others seem to us to be too broad in their conception, and if followed literally might involve a large number of unsuitable patients in getting this temporary fillip to their morale. On the occasions when we have relented in our limited criteria, both we and the patient have generally agreed in retrospect that it was not a good idea On the few occasions in which we have relented without subsequent regret, it has been because we have given a short course for a pre-arranged period and for a specific purpose Most important of all, we have obtained in advance the complete co-operation and understanding of the patient concerned.

As an example of this we could quote the chair-bound arthritic lady who was determined to carry out a concentrated period of social engagements which were vital to her husband's career Her anxiety lest she should be too crippled to stand at the various receptions seemed to us to be a reasonable justification for helping her over this stressful period But we did so on the strict understanding that she was not suitable for long-term therapy, and would almost certainly relapse completely when we withdrew the drug

Her stoicism and well-integrated personality were other factors which we took into account in agreeing to help her in this way Our confidence in her was well rewarded by her overwhelming gratitude and we have been able to help her in this way on subsequent occasions

Indeed, if we could have found a simple way of defining this type of case we would have included it as a third unexceptionable criterion for short-term therapy Since, however, in each case there are so many diverse factors to be considered it is a problem which is best left to the discretion of the physician in charge

With regard to the other two unexceptionable criteria, the first—episodic rheumatoid arthritis—is self-evident but extremely important. There are, broadly speaking, two different varieties of episodic arthritis The first, which is also known as palindromic rheumatism, consists of a series of short sharp bursts of activity interspersed with

periods of *complete quiescence* Sometimes these episodes occur with remarkable regularity so that the patient can predict in his diary for months ahead the days when he is likely to be *hors de combat.* In some women the rhythm may bear some definite relation to the mens-

comes evident that his progress has been in the form of a series of

patient gradually becomes more crippled with each attack.

Unfortunately the distinction is a little artificial since both varieties

allow each episode to progress unchecked save by orthodox measures Since this can be done with very little risk of causing complications (unless the episode happens to be a particularly long one), we consider that in the absence of an obvious contra-indication all cases of episodic rheumatoid arthritis should be treated with cortisone or one of its analogues.

The second of Hench's indications with which we agree unequivocably, referred to its use for covering an intensive period of rehabilitation or an orthopædic manœuvre such as manipulation and its subsequent physiotherapy

We cling to this belief despite the evidence of a controlled trial published in 1954 This trial concerned manipulation of the knee joint

received manipulation, physiotherapy and codeine.

Whilst we have no particular criticism of this trial, we feel bound to record that its results do not accord with our own experience. In addition, we have sought the opinion of many of our orthopædic colleagues who have had considerable practical experience in this type of therapy We found that, with varying degrees of enthusiasm, they agreed with us that the reactionary pain and spasm which occur following the manipulation of arthritic joints can be largely suppressed if adequate doses of cortisone are given Not only is this far more

pleasant for the patient, but it enables the physician

time and both he and the physiotherapist have

For example, it is not uncommon to find a patient who has learned to

this purpose, it is quite legitimate to use a short course of steroid therapy, provided that the patient understands completely the object of the manœuvre. We have had both successes and failures when using cortisone for this purpose, and we wish to stress that we do not recommend is as a *routine* procedure, but as an *occasional* method of helping an ambitious but frustrated patient

15. Does Steroid Therapy ever provoke or delay a Natural Remission or Relapse?

This problem has been hinted at several times in the course of our discussions. However it is a point of such fundamental importance that it deserves separate recognition even though we can produce little factual evidence to support our opinions.

It is our firm conviction that these drugs have no specific action on the natural remissions which characterize this disease. Accordingly

in any event, albeit far more gradually.

By contrast, we do not subscribe to the view expressed by one American authority that the incidence of natural remissions is less than normal in patients who receive long-term cortisone therapy. We have stressed that the recognition of such a remission is more difficult when a patient is receiving full suppressive treatment, but that they occur with normal frequency, we have little doubt.

Apart from the well-recognized rebound relapse which occurs if the drug is withdrawn too rapidly, we do not believe that there is any conclusive evidence that cortisone causes any other form of relapse.

There are, however, some who believe that a systemic spread of the disease is more common in cortisone-treated patients than in the untreated.

tion and visceral spread of the disease, is one which has for long been recognized as an occasional mode of deterioration in untreated rheumatoid arthritics. Patients who relapse in this way eventually merge imperceptibly into the syndrome of disseminated lupus erythematosus. They may even manifest the so-called L E cells when their serum is appropriately incubated.

The only points which remain to be settled, therefore, are whether these changes occur significantly more frequently in patients who are treated with cortisone than in a comparable group of rheumatoid arthritics receiving no specific treatment and, secondly, whether they are reversible once they have occurred. Both these points are in the

to ignore it as a hazard in practice

16. The Clinical Deficiencies of Cortisone

Instead of trying to summarize all that we have said about the

possibility is a measure of the rapid developments in our thoughts about the problems of therapy in rheumatoid arthritis

The Ideal Drug .	*Cortisone :*
(1) Must consistently reverse the disease process as well as the signs and symptoms	Reverses the signs and symptoms, but has no effect on the fundamental disease process.

(ii) Must be proof against relapse when the drug is withdrawn.	Consistently allows a relapse to occur. In addition it *frequently exhibits* a "*rebound*" effect if the drug is withdrawn too rapidly.
(iii) Must not be subject to habituation or tolerance.	Frequently exhibits evidence of these phenomena in practice. The possible explanations are discussed fully in the text.
(iv) Must not become a drug of addiction	Occasionally gives rise to complete "dependency"—perhaps "addiction" is too strong a *word This feature assumes* importance in relation to the vexed question of "hypercortisonism".
(v) Must have a wide, predictable and constant toxicity: therapeutic ratio	Has a completely unpredictable ratio which in many cases is disconcertingly narrow.
(vi) Must not be associated with any metabolic upsets within the therapeutic range	The metabolic complications seem inextricably woven with the therapeutic effect of the *drug*
(vii) Must be simple to administer.	Can be given orally and is, therefore, simple. It would be preferable if it could be given in a single dose instead of having to be administered three or four times a day
(viii) Must be suitable for out-patient administration by general practitioners	Can be started as an outpatient, but it is preferable to arrive at a maintenance dose while the patient is under close observation at hospital. Needs laboratory and x-ray facilities Therefore not ideal for general practitioner use.
(ix) Should reverse symptoms without producing sedation.	On the whole fulfils this criterion, but may cause undesirable psychomotor stimulation

(x) Should be specific and, therefore, of help diagnostically—on the analogy of colchicine in gout.	Has a very wide range of therapeutic activity and is by no means specific
(xi) Should have a consistent action on one or more laboratory anomalies, which could be used as a basis for controlling the dosage.	Has no such reliable action and no test is available which will replace experienced clinical judgment as a means of controlling the dosage
(xii) Should not only reverse the active disease process, but also help in dealing with the existing joint destruction.	Has little or no effect on existing joint destruction except, possibly, to aid rehabilitation procedures
(xiii) Should be cheap and easy to produce in bulk.	Is expensive and difficult to produce in bulk.

17. Suggested Plan for the Distribution and Administration of Cortisone

Many adrenal steroids are now freely available to general practitioners While in principle this is an excellent thing, there is no doubt that close liaison between the general practitioner and hospital clinics is essential for optimum results

We consider that the situation is remarkably analogous to the problem of looking after diabetics, in which speciality a very happy relationship has grown up between the specialist clinic and the general practitioner. Accordingly we believe that cortisone clinics should be set up at convenient hospitals and that every arthritic who is treated [illegible]

[illegible]

two- or three-monthly intervals

(*c*) To be available at all times to deal with the complications or problems that arise which are outside the experience of the practitioner

(*d*) To keep careful records as a basis for investigation into the vexed and important problem of case selection Until this can be determined on an objective, as opposed to intuitive basis, cortisone therapy is bound to remain a gamble in many cases

(*e*) To try out any new drugs for which anti-rheumatic properties are claimed, before they are released to the rest of the profession

CHAPTER 5

INTRA-ARTICULAR INJECTIONS OF CORTISONE AND HYDROCORTISONE

THE history of therapeutic intra-articular injections in rheumatoid arthritis in the pre-cortisone era was both sporadic and disappointing.

To mention but a few attempts: liquid petrolatum, lipiodol, procaine hydrochloride, lactic acid and acid sodium phosphate have had evanescent vogues, but none is still in general use and there is little or no objective evidence that they act as anti-inflammatory agents.

It is reported that Thorn in Boston was the first to inject hydro- [illegible]

After Thorn's single injection of hydrocortisone, the early research was performed almost entirely with cortisone. Hydrocortisone was not available in quantity for about two years.

Using a cortisone acetate suspension, most authorities claimed a significant response in rather less than 25 per cent. of cases. As soon as it was appreciated that hydrocortisone was the natural anti-inflammatory secretion of the suprarenal cortex, the manufacturers turned their energies to the even more complex production problems associated with this drug, and by 1951 small quantities were becoming available for research purposes

At once, its superiority over cortisone was appreciated whether it was used in the form of its acetate or as the " Free Alcohol ".

It was claimed by Hollander that partial suppression of inflammation occurred in 90 per cent. of cases within 24 hours of the injection, that the duration of benefit averaged about eight days with a wide and unpredictable range from about forty-eight hours to several weeks. No systemic e[illegible]
injections seer[illegible]
original one. [illegible]

subjective assessments.

It could be argued that since constantly repeated intra-articular injections are impossible in most cases, for purely practical reasons,

and since in the majority of cases the improvement is evanescent, there is no justification for using hydrocortisone in this way as a routine therapy. The injections are always unpleasant and sometimes painful, they are time-consuming to perform, the material is expensive, and the risks of infection and other technical catastrophes have always to be considered however slight they may be in practice.

Yet despite all these perfectly legitimate objections, the current fashion for this form of therapy has positively snowballed since hydrocortisone first became available. One of the reasons for this is that in a small group of cases the improvement after each injection lasts considerably longer than indicated above—sometimes a matter of four to six months—and very occasionally a single injection may be enough to provoke permanent remission in an inflamed joint.

Unfortunately, however, there is no way of predicting at the moment which cases will behave in this way nor why they do so. Such results are very impressive when they do occur, and it seems that optimism rather than logic must to some extent lie behind current enthusiasm

It is safe to predict that the pendulum will swing back again within the next year or two Eventually the aim must be to produce a test which will enable the good responders to be detected so that we no longer have to rely upon trial and error.

Indications

Despite objections to intra-articular therapy, there are certain specific and generally accepted indications for using it, and these will now be summarized.

(i) In patients in whom one or two accessible joints are predominantly affected, especially when such joints are the cause of disproportionate pain and disability. This situation is frequently seen when the knees are the worst affected joints.

(ii) [illegible]
in wh [illegible]
believe [illegible]
aspect [illegible]
the whole condition improves.

(iii) In elderly, infirm or other patients to whom the oral ad- [illegible]

[illegible]

(vi) As a preparation for, or after treatment by, orthopædic surgery and manipulation.

(vii) To reduce the size and discomfort which often arises from swollen bursæ arising from joints and tendon sheaths.

Disadvantages

The principal disadvantages of this type of therapy, apart from its temporary nature, are·

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techniques.* However, hydrocortisone is remarkably innocuous if not accurately placed, and seldom results in anything more serious than a temporary local pain and soreness lasting about forty-eight hours.

(iii) Approximately 2 per ce
tivity response to the drug and
hours following the injection.
serious, since it always seems
treatment.

(iv) The injection of hydrocortisone by mistake into a tuberculous joint has been reported In at least one case a fatal miliary spread of the disease occurred as a direct result of this mistake. Similar

who reported four cases of septic arthritis of the knee joint and two of the hip joint within his personal experience. This author naturally commends an ultra-cautious attitude, and such strict aseptic precautions as would virtually preclude the injections being carried out as a ward or consulting-room procedure

However, Hollander and his group report that their incidence of the same complication was only two cases of sepsis in a series of 8,000 injections, and that both of these cases were easily controlled by the appropriate antibiotics The only precautions which they advocate are " careful instrument technique and thorough skin cleansing ". In particular they do not feel that the wearing of sterile gowns or gloves are necessary, nor do they use a local anæsthetic in the skin in most cases The majority of clinics in this country appear to conform more to Hollander's standards than to the more rigid " No touch " techniques, if only for practical reasons

We do, however, recommend the use of local procaine anæsthesia, partly out of deference for the patient's comfort and partly because by doing so one is enabled to use a larger needle and to aspirate the joint before injection We feel that this procedure consideraby potentiates the effect of the hydrocortisone, especially when a very large or tense effusion is present Unfortunately, however, it does take considerably longer to perform a complete aspiration and this often renders it impracticable.

(vi) Finally, it must be stressed that the only type of joint in which

* See Appendix.

it is reasonable to expect hydrocortisone to prove effective is one

of the injection

To inject it, as is frequently done, into a chronically deranged joint whose thickened tissues represent "burnt-out" inflammation and whose synovial "fluid" has the consistency of thick cream cheese, is to betray a profound ignorance of the action of the drug. Occasionally the patient may claim a temporary subjective relief from such an injection, but a significant objective improvement is out of the question.

DOSAGE REQUIREMENTS

These seem to have been worked out on an empirical basis. We believe that the schedules recommended in the original papers and copied into the current textbooks are rather niggardly. They may have been influenced originally by the very difficult supply position which used to exist

In point of fact, there appears to be little risk of overdosage, and apart from the mechanical discomfort which may result if the bulk of the

done.

Accordingly we recommend the following schedule.

Hip joints Knee joints	4–6 ml	100–150 mg
Ankle joints	4 ml.	100 mg
Elbows Shoulders	3 ml	75 mg
Wrists	2 ml	50 mg.
Mid tarsal joints Acromio-clavicular joints Temporo-mandibular joints Sterno-clavicular joints	1 ml	25 mg.
Metacarpo-phalangeal joints Metatarso-phalangeal joints Interphalangeal joints	5 ml.	12 5 mg.

Sometimes it is convenient to dilute the hydrocortisone and this can be effected quite simply with 1 per cent procaine. Quite recently a fashion has developed in some centres of adding 1,000 units of hyaluronidase as well The benefits claimed for this measure are that it

which problems of exact localization are more common than in intra-articular work.

We have had little experience with this type of combined therapy, but on theoretical grounds it seems to be very illogical, since one of the *acknowledged actions of hydrocortisone is its specific* "anti-hyaluronidase effect."

RESEARCH ASPECTS

Apart from the purely clinical aspects which have just been dis-

1. *Q. What evidence is available that hydrocortisone has an anti-inflammatory action?*

   A. (i) It greatly reduces the total white cell content of the synovial fluid and simultaneously alters the lymphocyte : polymorph ratio in favour of the former.

   (ii) Synovial biopsies after injection show a definite diminution of inflammatory infiltration

   (iii) The viscosity of the synovial fluid—usually very low in actively inflamed joints—rises rapidly towards normal. The low viscosity is said to be due to a depolymerization of the mucopolysaccharides in the fluid. Hydrocortisone appears to be capable of effecting a repolymerization of these substances

   (iv) In inflammatory fluids, there is an increase in concentration of a specific enzyme known as aminotripeptidase Its level is roughly proportional to the amount of cellular infiltration in the fluid and surrounding tissue It is consistently reduced, often to normal levels, following hydrocortisone injections.

2. *Q. How long does the hydrocortisone remain in the joint after it is injected?*

   A. A series of "recovery" experiments were carried out in order to establish this point The results showed a very remarkable rate of disappearance.

   Five minutes after the injection, only 60 per cent. could be recovered.

   Thirty minutes after the injection, only 21 per cent and

   three hours after the injection only 2 per cent.

3. *Q.* [illegible] *evidence*

   A. (i) *Hydrocortisone has been put into a knee joint about one* hour before it was due to be opened surgically. At operation, sections of synovial membrane were removed, the

steroids were eluted and then analysed It was fo
that a substantial proportion of the injected steroid
firmly incorporated in the membrane.
(ii) Subsequent studies with radioactively labelle
hydrocortisone revealed with considerable accuracy h
much remained in the fluid and how much had been

greater within the fluid than in the cells.

4. *Q*

A

potency cannot be explained on the basis of their diffe
solubilities and the varying rates of absorption which m
result from this
(ii) By contrast, if the concentration of steroid *in*
synovial membrane was estimated following identical d
of the two drugs, it was found that hydrocortisone
stored in about double the concentration as compared
cortisone In this startling fact may lie a very import
clue about their relative potencies.
(iii) Another suggestion was that cortisone had to be c

does not.

5 *Q*

injection into the synovial cavity?

A The answer to this question is unfortunately "No".
reason, however, is certainly not for want of trying b
due to the technical limitations already mentioned w
preclude the accurate identification of many of the m
bolites found on a chromatogram. In the future lies
hypothetical but very real possibility that we may be abl

identify not only each stage in the breakdown but the enzyme which is responsible for it. The practical applications which could stem from this knowledge are immense. We might even find that one of the simpler breakdown products worked just as effectively as the parent substance. On a more acade- [illegible]

that the synovial membrane is capable of effecting a chemical transformation in certain steroid compounds which have been injected into it. What we still do not know is whether the transformation is due to the membrane *per se* or to the inflammatory cells which infiltrate it. Nor is it certain that such a conversion is essential to therapeutic potency. It is believed that the metabolites found in the fluid are the result of back diffusion from the synovial membrane.

6. *Q.* *What of the newer drugs?*

A. A number of analogues and esters of hydrocortisone have been tried out by Hollander's group in the United States. Of these, only hydrocortisone tertiary butyl acetate appears to be superior to the parent compound, especially as [illegible]

preparation despite a failure to benefit from hydrocortisone acetate.

It is too early to say yet whether prednisone and prednisolone will be effective in local therapy, although there are encouraging reports from abroad. It is understood that they will shortly be available in this country for clinical trial. The 9-alpha-fluoro esters are unfortunately too dangerous for local use because of the very marked fluid retention which they cause.

CHAPTER 6

THE USE OF CORTISONE IN DISEASES OTHER THAN RHEUMATOID ARTHRITIS

Throughout this book so far, we have confined our attention to the [illegible]

[illegible] ultimately progressive diseases for which steroid therapy often seems to be indicated. It is also the group in which most of the difficulties arise since long-term, continuous therapy is usually essential The problems related to the *drug aspect* of therapy are similar, if not identical, in other diseases in this group. Therefore, in this section we can [illegible]

[illegible] otherwise have been possible.

The third and most cogent reason is that the author's personal [illegible]

[illegible] ences available to us.

We shall divide our review into the following three categories:

I. Other rheumatic disorders
II. Para-rheumatic disorders.
III. General medical conditions:
    A. Dermatological diseases
    B. Gastrointestinal diseases
    C. Respiratory diseases.
    D. Renal disease.
    E. [illegible]

drugs which were sufficient for essential purposes, but grossly inadequate for unrestricted distribution. They therefore issued, on the

state, etc.)

(ii) Pituitary deficiency (Simmonds' disease, etc.).
(iii) Lupus erythematosus (systemic forms).
(iv) Polyarteritis nodosa.
(v) Pemphigus.
(vi) Exfoliative dermatitis.
(vii) Sarcoidosis.
(viii) Congenital adrenal hyperplasia.

We do not commend this list as being exhaustive, nor do we believe that all cases of the above diseases would *of necessity* require hormone treatment. It is an interesting list, however, as it includes most of the conditions for which, on occasion, cortisone has a life-saving potentiality

We may now return to our survey of individual diseases for which cortisone may be required.

I. *Rheumatic Diseases other than Rheumatoid Arthritis*

(i) **Acute Rheumatic Fever.** The assessment of therapy in this condition is notoriously difficult since one is dealing with the effects of the drugs on the immediate signs and symptoms of the disease and is also concerned with their remote effects in relation to the development of chronic carditis.

In some cases this does not manifest itself for many years after the acute illness, and indeed, the severity of the heart lesion does not correlate at all well with the intensity of the original attack. It will there-

period.

We know from recent histological studies performed on left atrial appendages removed during valvulotomy operations that our clinical indices of activity are crude. For example there can be histological evidence of rheumatic activity, in the form of Aschoff bodies, in cases who have long since been considered to be quiescent from a clinical point of view.

Despite all these difficulties, there have been some detailed controlled

studies, culminating in a co-operative study in which six British and five American centres took part. This trial set out to compare the

steroid group to relapse for a limited period on cessation of treatment

judgements. The omens, however, do not look very hopeful as regards the superiority of the new forms of treatment over the traditional.

As soon as these results were published there were the inevitable crop of criticisms about the conduct of the trial, notably about the rigidity of the dosage schedules and the fact that the treatment had to be cut after an arbitrary period, and not as indicated by the individual case.

Coupled with these detailed criticisms were the convictions of many prominent specialists in rheumatic fever on both sides of the Atlantic that these drugs do play an important part at least in individual cases of rheumatic fever. Reports of dramatic recoveries in patients who had congestive heart failure, who would probably have died had they been treated with salicylates alone, lent force to these convictions.

We are now awaiting the results of a series of trials in which very much higher doses for very much longer periods have been used. Preliminary results have been published and give some grounds for optimism In addition, the advent of prednisone has removed one of the hazards of this type of therapy, namely that the embarrassment to the heart from the drug-induced sodium retention might outweigh the

orthodox treatment in cases of acute rheumatic fever, we argue as follows, on the basis of simple logic and a limited experience of looking after these cases in a rheumatic fever unit in New York:

In cases who show no clinical evidence of cardiac involvement, it possibly does not matter whether they are treated by salicylates,

carditis can occur in an asymptomatic disease, it seems reasonable to assume that it may occur with even greater facility during an acute

Our choice

its scientific

alizations in

support of our personal views.

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and duration of this inflammation, the subsequent scarring might also be minimized. Therefore, the risk of ultimate stenosis or incompetence should be lessened.

We have already recorded that certain unequivocal manifestations of inflammation such as the rheumatic nodule, the systolic murmur and the raised sedimentation rate, resolve significantly more rapidly with hormones than with salicylate treatment. More recently, two American authorities have published results showing that if high-dosage therapy is instituted within a week of the onset of symptoms, carditis will be rapidly relieved in 84 per cent. of cases, and only 6·4 per cent. will be left with signs of cardiac damage at the end of their attack. However, if therapy is delayed beyond this period, the incidence of delayed cardiac disease is about 49 per cent. The dosage advocated in the latest American publications ranges between 300 mg./day for six to eight weeks in one series and 500 mg./day for two to three weeks followed by a slow decrease until all the signs of disease activity have abated. A fall in antistreptolysin titres is said to be a good guide to cessation of activity.

The matter is still *sub judice* and we have had little experience in this country of the use of such large dosages In spite of this, however, we feel confident that the steroid drugs will eventually prove to be the

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involvement

(ii) **Ankylosing Spondylitis.** In the pure form of this disease, the arthritis is mainly confined to the spinal column and the sacro-iliac joints, with occasional involvement of the hips, the shoulders and the knees. We shall confine our discussion in this section to this type, in contradistinction to the mixed peripheral and central syndrome which is more commonly seen in the United States of America, and which

the large majority of

g therapy are largely

d stiffness and, as a

corollary of this, the prevention of deformity and ankylosis of vital

for a short time in order to cover an intensive period of rehabilitation or an orthopædic manœuvre.

which seems so self-evident, because of the surprising frequency with which this type of patient is referred to us for advice as a "failed cortisone case".

In a published study comparing the effect of cortisone and deep x-ray on the dr her. These ted, despite some early experimental work on animals which suggested that the risks of radiation sickness might be enhanced by cortisone. In some cases, their combined use appears to have a complementary effect on the patient.

In about 20 per cent. of spondylitics, iritis or iridocyclitis is liable to occur at some time as a complicating factor. This inflammatory lesion responds very well indeed both to local and to systemic steroid therapy.

One word of warning: The incidence of peptic ulceration in ankylosing spondylitis is said to be significantly higher than in the general population If this is so, it is possible that the use of prednisone and its derivatives will be contra-indicated in this disease in view of the notorious reputation which these drugs have for causing peptic ulceration even in non-predisposed people. It is too early to dogmatize yet on this point on the basis of our limited experience.

To summarize these points; it seems as though steroid therapy will be the drug of choice in an even smaller percentage of cases of ankylosing spondylitis than the 10–15 per cent. which we estimated for rheumatoid arthritis Its main indications are in early and progressive cases which cannot be otherwise controlled or to cover short periods of intensive physiotherapy or an orthopædic manœuvre. Finally, it is almost always indicated locally or systemically in cases of iritis or iridocyclitis.

(iii) **Juvenile Rheumatoid Arthritis: Still's Disease.** This disease may remain active for many years and may even continue beyond puberty

develop as a result of interference with epiphyseal growth processes. As in the adult form of the disease, cortisone can be very helpful in preventing the former hazard, especially in association with appropriate physiotherapy and splinting.

It was feared at one time that it might have an adverse effect on epiphyseal development because a general retardation of growth had been reported when these hormones were administered to young and growing animals for prolonged periods However, these fears have proved to have been unfounded in practice, though it is not yet clear

whether steroid hormones can accomplish the reverse and stimulate normal growth to take place by suppressing the inflammation which inhibits the epiphysis.

Another frequent complication seen in prolonged attacks of Still's disease is the development of amyloid changes. Here again the effect of cortisone on amyloidosis is far from clear. One or two well-authenticated reports have appeared describing the onset of this [illegible] g cortisone. How- [illegible] this phenomenon [illegible] onfirmed, it would [illegible]

[illegible] neutropenia and lymphadenopathy (in adults "Felty's syndrome"), marked improvement in all these features has been reported from [illegible]

[illegible]

—in the case of babies—mobilizable.

For small children, it is usual to start at about a half of the equivalent [illegible]

[illegible]

any harm. [illegible]

[illegible]

all. [illegible] atients [illegible] post- [illegible] given

in any individual case may be a difficult one involving a weighing-up of many different factors.

(v) **Intermittent Hydrarthrosis and Palindromic Rheumatism.** These

therapy when the condition is widespread In doing so we almost certainly will not alter the natural history of the disease significantly, but we have already expressed the opinion that when these drugs can be used as suppressors of symptoms without taking any risks, it is justifiable to do so. This is an excellent example of such a symptomatic and safe application In addition to this, one occasionally seems to upset the intrinsic

episodes. The pat

appreciable time.

but in our experie

condition has been discussed more exhaustively in an earlier chapter.

(vi) **Reiter's Syndrome.** This, being an acute, and usually self-limiting polyarthritis, associated with urethritis, purulent conjunctivitis and keratodermia blennorrhagica, should be an ideal condition for

not use it routinely nowadays.

The published literature on the subject is a little confused, but we cannot do better than to quote from the latest edition of Comroe's textbook of Arthritis, which states categorically that steroid therapy should not be tried in these cases ". . at least until antibiotic (usually

(vii) **Gout.** One of the earliest properties of cortisone to be fully described was its marked uricosuric action This, combined with its potent anti-inflammatory properties, naturally gave rise to high hopes

whether steroid hormones can accomplish the reverse and stimulate normal growth to take place by suppressing the inflammation which inhibits the epiphysis.

Another frequent complication seen in prolonged attacks of Still's disease is the development of amyloid changes. Here again the effect of cortisone on amyloidosis is far from clear. One or two well-authenticated reports have appeared describing the onset of this complicatic [illegible]
ever other [illegible]
under the i [illegible]
represent in its own right a strong indication for treating all persistent cases of Still's disease with cortisone.

When rheumatoid arthritis is associated with splenomegaly, neutropenia and lymphadenopathy (in adults "Felty's syndrome"), marked improvement in all these features has been reported from cortisone therapy. Pyrexia and pericarditis are other features which are [illegible]

[illegible] adult

[illegible] ease

[illegible] For example we

any harm.

[illegible]

case is excessively difficult, and unless the [illegible]

[illegible]

all.

Unfortunately it occurs predominantly in just that group of patients whom we have stigmatized as doing badly on these drugs, namely post-menopausal females, so the decision as to whether it should be given

as soon as an intravenous infusion of corticotrophin was commenced. We have no accurate knowledge of how it works in this condition, except that it seems to "insulate" the skin, liver and bone marrow temporarily from the circulating gold whilst it is being eliminated.

(x) **Osteoarthritis.** We can state with complete conviction that there are no indications for the *systemic* use of these drugs either in

elieve that the mis-

l osteoarthritis (as

l arthritis, is a not

infrequent cause of so called "failed cortisone therapy"

By contrast to this rather dogmatic statement, we believe that there are many and important indications for the *local* use of hydrocortisone acetate in osteoarthritic joints If these are judiciously selected, we

Accessibility is another factor which is important in choosing this

and ankles. One of the best joints to treat is the first carpometacarpal joint of the hands, which is so frequently afflicted by a painful and intractable form of osteoarthritis, especially in women.

Unfortunately, for technical reasons, this type of injection therapy is not practicable in the osteoarthritic joints which cause so much pain and disability in the vertebral column.

It is impossible to predict in any given case how long the relief will last, but it is likely to be far longer than with active rheumatoid arthritic joints. The doses, however, are exactly the same as with this disease and will be found on page 85.

We would stress again, in conclusion, that it is futile to expect good results from the injection of chronic degenerative joints with advanced radiological changes by hydrocortisone solutions Such joints at best can only respond by short periods of largely subjective relief.

(xi) **Non-Articular and Peri-Articular Rheumatism.**

(A) *Systemic Therapy.* Many of the original claims for cortisone, especially in the lay press, were that it was a cure for "rheumatism". To the layman the term rheumatism represents a homogeneous entity which includes the entire range of painful musculo-skeletal disorders. Hench once defined the term as "Any pain occurring within a mile of a joint!"

Needless to say, there resulted an immediate invasion of hospital clinics and private consulting-rooms by the hosts of perennial sufferers who form the solid core of rheumatological practices, all staking their claims to treatment by the new wonder drug.

Whatever diagnostic classification we use to describe these patients, there is usually a small residue for whom we are forced into the

that here at last was the ideal drug with which to treat and prevent acute attacks of gout.

The almost simultaneous discovery of two other potent drugs for the treatment of this condition, and the fact that cortisone therapy had one serious drawback, led to its rather precipitate abandonment before it ever came into general use.

The unexpected snare which ruined its reputation was its tendency to allow a rebound attack if withdrawn prematurely. Sometimes the withdrawal attack was more severe than the initial one which it suppressed, and this led to a vicious circle and a therapeutic quandary as [illegible]

an acute attack of gout, colchicine in doses of 0·5 mg. t.d.s. should be [illegible] simultaneously.

[illegible]

phenylbutazone have more or less rendered it a superfluous drug for this purpose. Phenylbutazone can be given intra-muscularly in larger doses than are considered safe when it is administered in chronic conditions, since the dangers of toxic effects are negligible when it is [illegible] for a few days at a time. It is an extremely effective drug in [illegible]

the same result [illegible]

using hormone therapy over a long perod (if not permanently) in these patients.

Although for these reasons cortisone and its derivatives have been ousted from a practical point of view in the routine therapy of gout, it is wise to remember their potentialities for those rare cases who do not [illegible] to other drugs, or when an even quicker response than they can [illegible]

certainly warrants a separate mention. It is a little ironical that one of the unequivocal uses of the new drug is to cover up the deficiencies of its most important predecessor. However the fact remains that in serious forms of gold poisoning, the administration of soluble corticotrophin is urgently indicated. It seems to protect the patient during the appreciable period before British Anti-Lewisite starts to take effect.

We have seen several cases who in our judgement would certainly have died, in the presteroid era, making the most remarkable recoveries

We try to select patients in whom the shoulder movement is limited by pain and spasm (more than by adhesions). Such joints are usually also tender to firm pressure. A patient in this phase usually finds it too painful to carry out effective mobilizing exercises, therefore the capsule becomes progressively more adherent. In these circumstances, and

seems to act more quickly and there are fewer rebound phenomena

could be obtained by intensive physiotherapy alone. If not, we usually arrange for a manipulation under anæsthesia on about the fourth day. It is vitally important in our opinion that the physiotherapist should

continued in doses of 40 units per day for another three or four days. It is then decreased by 10 units per day until it is withdrawn entirely between the eleventh and twelfth day.

which for obscure reasons undergo a spontaneous resolution fairly

periarticular affection of the shoulder, associated with a severe and disabling vasomotor upset in the hand. In some cases it appears to represent merely an extension of the pathology of the "frozen shoulder" which we have just described, but more frequently it is associated with a cardiac disorder such as a coronary thrombosis. It is an intensely

unsatisfactory label of " chronic muscular rheumatism "—colloquially known as " fibrositis ".

It is interesting to reflect and to try to explain how the confusion

ganda, and the fact that this diagnostic group includes a high percentage of cases of " psychogenic rheumatism ", these cases being notoriously suggestible to any new form of therapy.

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the most experienced clinicians. It is therefore probable that some of these—who would be expected to respond well to cortisone—were included in the early claims.

This point is emphasized in mitigation of an otherwise categorical statement of our opinion that there are no indications whatsoever for the *systemic* use of cortisone or its analogues in non-articular forms of rheumatism

Periarthritis. With regard to periarticular conditions, the one which immediately springs to mind is periarthritis of the shoulder colloquially known as " the frozen shoulder ". Here again we are in a

in this condition.

From our experience, we would conclude that in the chronic stage of periarthritis of the shoulder—which is often painless—systemic cortisone is unlikely to be of any help in hastening recovery. However, in the acute and painful phase, it is our impression that a short course of cortisone or corticotrophin will provide symptomatic relief and will help the physiotherapist in her efforts to prevent the shoulder becoming stiff.

lations in the acute or sub-acute phases of the condition.

We cannot truthfully claim that early manipulation under a " cortisone umbrella " is invariably successful as so much depends on the co-operation of the patient and the enthusiasm of the physiotherapist following the manipulation. We are confident, however, that we never reduce the patient's range of movement by this treatment, and this used to be the risk of early manipulation before these drugs were available.

soon as the patient returns to the occupation which caused it. It is

very painful unless they become tense. However, they are frequently very uncomfortable, inconvenient and unsightly for the patient. To

monly requires treatment are the ulnar olecranon bursa, the bursa arising from the dorsal tendon sheaths of the wrist and ankle, and the ischial and trochanteric bursæ

The "Rotator Cuff Syndrome" at the Shoulder including Subdeltoid Bursitis and the Supraspinatus Syndrome. The results of injection around the shoulder depend to a considerable extent on the exact localization of the lesion. As a corollary, if the lesion consists of a widespread degeneration, injection therapy of any sort is likely to prove useless.

The lesion which responds better than any other round the shoulder is acute or subacute supraspinatus tendinitis. In the majority of cases, one injection of 25 mg. hydrocortisone will completely cure the condition if it is accurately placed. Sometimes it is also desirable to inject around the biceps and coracobrachialis tendons which are frequently very tender in this condition.

Acute subdeltoid bursitis responds very dramatically to an injection accurately placed into the bursa. However, in the chronic adhesive variety we have not been impressed with the results of injection therapy, nor have we always found it easy to be certain that we were in the bursa.

In our hands, chronic bursitis of the shoulder, "frozen shoulders" as described in the last section, responds very poorly, if at all, to local injections into the joint cavity

Acute Ligamentous and other Soft Tissue Sprains. We have had little personal experience with athletic or other traumatic injuries, but there seems to be general agreement amongst those who do treat these conditions that recovery can be considerably hastened if a mixture of hydrocortisone, hyaluronidase and procaine is infiltrated into the injured tissue. We should, in fairness, add that at least one acknowledged authority on the subject considers that equally good results are obtainable by the use of the procaine and hyaluronidase alone, and that the use of the hormone is superfluous. A carefully conducted trial is required to settle this point finally. We have used hydrocortisone injections in cases of chronically persistent ligamentous strains with very satisfactory results.

Localized "Muscular Rheumatism." Although the pathology is completely unknown, we cannot blind ourselves to the fact that we meet occasional cases of acute localized muscle pain and tenderness. Very often it is possible to eliminate this local area of pain completely by an injection of procaine. However the relief is usually evanescent,

is strongly indicated. For obvious reasons, few of these cases will be fit for the rigours of manipulation or indeed anything more than the mildest of physiotherapy.

(B) *Local Therapy with Hydrocortisone.* There are many non-articular and peri-articular conditions which benefit considerably—sometimes dramatically—from the local injection of hydrocortisone acetate. These injections are usually not difficult to perform, but naturally the more accurately they are placed, the better will they succeed. Careless or ill-considered techniques are therefore to be deplored.

Sometimes it is desirable to increase the bulk of the injection by diluting with procaine and as has been described in another context, there is a recent vogue to add hyaluronidase to the injection in order to spread it more widely in the tissues.

The non-articular conditions in which this type of treatment is par-
ticula

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and g
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anæsthetize the entire area of tenderness in order to guarantee a successful result. If it is necessary in order to achieve this, we sometimes use double the quantities mentioned above.

We always warn the patient that it may be extremely painful for

a second injection are included. Usually
dis-

disabling condition.

De Quervain's Stenosing Tenovaginitis and other forms of Tenosynovitis. Many early cases of de Quervain's syndrome can be

ultimately satisfactory in most cases, although a relapse may occur as

(i) **Disseminated Lupus Erythematosus.** This disease can present in

ill health.

The decision as to whether such cases merit cortisone therapy on the basis of a laboratory test alone is a very controversial one, especially since the specificity of the test is considered suspect by many workers.

Our own attitude to such problems is to treat the clinical aspects of the disease on their own merits but to watch the patient very closely for

splenomegaly, hepatomegaly, hypertension, œdema, pyrexia, a spread of the rash or the development of purpura. These are all ominous signs of a dissemination of the disease usually demanding cortisone therapy.

This insidious type requires far more clinical judgment than one

By contrast, the *cerebral* signs and symptoms may prove to be extremely perplexing A liability to epileptiform seizures and to organic psychoses is a well-known hazard in this disease. Electro-

decide whether to reduce the dose on the assumption that the condition is drug-induced, or to raise the dose to formidable heights in an effort to control a suspected inflammatory process in the brain In one such case we have had to increase the dose as high as 600 mg. cortisone per day before our temerity was rewarded by a complete regression of the psychosis.

Our impression from seeing several cases of psychosis arising in this

and in these circumstances it is well worth while to repeat the injection with the "cocktail" recipe of hydrocortisone, hyaluronidase and procaine. Frequently [illegible]

[illegible]

underlying cause. The hyaluronidase should in theory help to spread the injection where the lesion is not completely localized but as has been noted, there is some doubt about this on theoretical grounds.

Temporo-Mandibular Arthrosis (or "the clicking jaw syndrome"). This is strictly an intra-articular rather than a soft-tissue use of hydrocortisone, but it is recorded here for the sake of convenience.

The pathology of the condition is not fully understood and the therapy usually unsatisfactory unless there is a specific and reversible dental anomaly causing a chronic strain on the joint. Intra-articular hydrocortisone has been tried in these cases largely on empirical grounds and on the assumption that there is a chronic inflammatory element. Apparently a small percentage of cases do respond very well and the therapy, although unpredictable, is always worth trying.

II. "Para-Rheumatic Diseases"

The term "para-rheumatic diseases" has been coined by an American group as a convenient alternative for the unwieldy term "Collagen vascular diseases". Under this heading, we shall discuss:

(i) Disseminated lupus erythematosus.
(ii) Scleroderma.
(iii) Dermatomyositis.
(iv) Polyarteritis nodosa,

[illegible]

selves to the major differences between them.

The outstanding differences are that, unlike simple rheumatoid arthritis, each of the four diseases in the present group is potentially [illegible]

[illegible]

Two conclusions may be deduced from these facts, in the first place, it is justifiable in these diseases to take far greater risks in selecting patients for treatment and in the dosage at which one is willing to maintain them. Secondly, there is no justification for delaying the treatment as one so often does with rheumatoid arthritis, in the hopes that a spontaneous remission will occur or a safer treatment suffice.

We shall now discuss a few specific points about each of the conditions of this group.

irreversible dense sclerosis and vascular obliteration, we have found the results of steroid therapy to be uniformly disappointing, and in our opinion the predominantly subjective benefits which it occasionally causes do not warrant the risks of long-term treatment. The only exception to this assertion is where the patient is severely embarrassed by symptoms representing the visceral spread of the disease.

These may be in the alimentary system causing dysphagia, from fibrosis of the œsophageal wall, cardiovascular from myocardial fibrosis or respiratory from fibrosis in the lungs Any one of these disabilities may become so unpleasant for the patient that they warrant at least a trial with cortisone to see if they can be lessened However symptoms

greatly

Needless to say, the improvement only lasts as long as the drug is administered and the risks of prolonged therapy do not differ significantly from those described in connexion with rheumatoid arthritis.

having weighed up all the relevant factors.

(iii) **Polyarteritis Nodosa.** Again in this disease, the response to therapy depends largely on the extent to which the pathology has progressed before treatment commences The basic lesion is an in-

determine the prognosis in any particular case.

It is agreed, however, that where parenchymal lesions in vital organs are not already established, these drugs may significantly delay their onset, and under ideal circumstances this can continue until a natural remission sets in.

By contrast, those aspects of the disease which appear to have an

left with little alternative but to try to suppress the underlying disease by using very high doses.

The *cardiac* and *renal* aspects of these cases often prove to be ex-

or they may be due to a hormone-induced salt retention and hypertension. Usually it is a mixture of both, and the exact interpretation and appropriate counter-measures must to some extent be a matter of guesswork and trial and error.

Unfortunately, as stated earlier, these drugs are quite valueless in *established* renal disease. It is this more than any other lesion which is liable eventually to kill the patient. It is difficult to be sure to what extent the early institution of suppressive therapy can abort this. Certainly it does not provide complete protection. However, the belief that it can slow down the remorseless march of events is the main justification for exposing patients almost routinely to the risks of this form of therapy.

Diseased kidneys are often unable to respond to cortisone normally by excreting potassium Potassium intoxication may therefore occur. It is consequently definitely unsafe to administer potassium to such patients in the ab

The *hæmatolog* of the disease, respond specially

therapy.

The question as to whether cortisone therapy influences the long-term prognosis in these cases is another controversial one. We believe that many of the fulminating cases who would undoubtedly die if left untreated can be suppressed until a natural remission occurs. It is unfortunately true that such patients are likely to get recurrent attacks, each one leaving behind its legacy of diffuse and irreversible tissue

it may sometimes be difficult to judge

n these circumstances it is

the serum hexosamine is a

cases of this condition with

indeed some of the bizarre forms in which it may present itself have only recently been described with the aid of biopsy material and electromyographic studies. Within the limits of our small experience

III. Non-Rheumatic Disorders

and some seem merely to have been frivolous. In this section we propose to review the subject briefly, confining ourselves largely to the conditions about which there is general agreement that steroid therapy is indicated

Since the dermatologists appear to be using larger quantities of these drugs than most other specialists it would be convenient to commence our systematic review within their orbit.

A. Dermatological Conditions

The pharmacological properties of cortisone which are probably invoked in dermatological practice have been listed in a recent review. They are:

(i) Acceleration of the capillary blood flow.
(ii) Raising of the skin temperature.

dc

co

rheumatic diseases " which we have discussed

with *erythema multiforme.*

allergic basis are very greatly benefited by cortisone. For example, manifestations such as asthma, joint and muscle pains, allergic skin reactions and eosinophilia can be very considerably improved.

[illegible] va [illegible] be [illegible] treatment including cortisone, implying probably that the vascular lesions have reached the occlusive stage before the symptoms draw attention to them.

In so far as the disease frequently affects young people and the sex incidence is about two males to each female, the problems concerned with cortisone administration may be rather less formidable than in some of the other diseases which have been discussed. We believe that most patients suffering from this condition deserve a short therapeutic trial with steroids in the absence of any major contra-indication. Treatment can then be maintained in patients who derive significant benefit.

The prognosis in general in this disease is very poor. Many cases die of renal or cardiac insufficiency or of intercurrent infection within a year. However there is at least one variety of the disease known as *temporal arteritis* which is usually an acute and self-limiting condition. *The pathology, which appears to be identical with that* of polyarteritis nodosa, is limited in this case to one or both temporal arteries. It is an intensely painful condition in the active phase and the response to cortisone can be highly dramatic. It is also a safe form of therapy since it seldom requires to be administered for long enough [illegible] cases.

(iv) **Dermatomyositis and Polymyositis.** Our own experience confirms most of the published reports that the response to cortisone and its analogues is extremely variable and unpredictable in these diseases. We have had patients who were entirely dependent upon it and who became virtually paralysed and bedridden when it was withdrawn. Others, who had involvement of their larynx and pharynx, were unable to swallow or speak properly unless they were receiving the drug. By contrast, we have had cases in whom the diagnosis appeared proven beyond reasonable doubt, who seemed to derive little or no benefit from large doses of these drugs.

[illegible] that at least two factors are concerned in deter- [illegible] symptoms is muscular weak- [illegible]

The syndrome of *polymyositis* is attracting considerable interest,

(a) Lichen simplex.
(b) Discoid eczema.
(c) Otitis externa.
(d) Anogenital pruritus.
(e) Atopic dermatitis.
(f) Seborrhoeic dermatitis.
(g) Sarcoid (by local injection into the lesion).
(h) Contact dermatitis.
(i) Ano-genital psoriasis (variable results).

The following conditions do not appear to respond significantly to local treatment with the ointment or lotion:

(a) Acne vulgaris.
(b) Alopecia areata.
(c) Exfoliative dermatitis.
(d) Herpes.
(e) Lichen planus.
(f) Lupus erythematosus.
(g) Pemphigus.
(h) Pityriasis rosea.
(i) Most forms of psoriasis.
(j) Rosacea.

Symptomatic relief in the responsive group often occurs very rapidly but may be delayed up to forty-eight hours. The ointment should be applied very frequently at first until the eruption is under control. Maintenance inunctions can generally be reduced eventually to two or three per week. As soon as the inunction stops, most of the chronic conditions tend to relapse in a matter of a few days. This form of therapy is naturally more practicable in conditions in which the lesion is more or less localized than where it is very widespread. It is virtually free of side-effects, and where these do occur, they are more frequently due to sensitivity to the vehicle in which the drug is made up than to the hydrocortisone itself.

(*c*) *Erythrodermas.* This is a mixed bag including those which are idiopathic, those which arise on a basis of seborrhœic dermatitis or psoriasis and those which are manifestations of certain

listed under (*c*) or the result of sensitivity to heavy metals or drugs. A permanent remission may occur in this condition, if the precipitating factor can be removed.

Relative Indications. We now come to a group of *dermatoses* which are far less serious than the ones we have just discussed; in addition most of them are self limiting. The decision about systemic steroid therapy must again be weighed in each case according to the amount of distress which the eruption is causing the patient and other clinical factors, always remembering that some of them may be controlled by topical therapy alone and this is almost devoid of risk. The conditions in this group include:

- (*a*) Simple drug eruptions.
- (*b*) Contact dermatitis.
- (*c*) The Stevens-Johnson syndrome.
- (*d*) Herpes zoster. Variable results are obtained in this condition; sometimes the pain vanishes dramatically within twenty-four hours, sometimes it seems not to respond at all. Indeed it has even arisen in patients who were taking cortisone for other purposes.
- (*e*) Neurodermatitis.
- (*f*) Atopic dermatitis (including infantile eczema and Besnier's flexural prurigo).
- (*g*) Idiopathic eczema.
- (*h*) Seborrhœic dermatitis.
- (*i*) Generalized psoriasis.
- (*j*) Lichen planus.
- (*k*) Resistant cases of skin sarcoidosis.
- (*l*)

the drug is withdrawn.)

from 0 25–2 5 per cent. For reasons both of economy and safety the weaker preparations should be prescribed initially. The majority of sensitive eruptions do not require more than 1 per cent and only a few peculiarly insensitive ones will require the 2 5 per cent. concentration.

Recently the results of an excellent controlled trial from the London

In the former, there is very little dispute that the steroid drugs represent a striking therapeutic advance in this distressing and occasionally fatal condition. Except in the most urgent cases, it is recommended that a reasonable trial be given initially to the traditional remedies such as subcutaneous adrenaline and intravenous aminophylline. If these fail, or if the patient is particularly distressed or shows signs of incipient cardiac failure, cortisone or corticotrophin

20 mg. per day as the attack is brought under control. Probably the quickest method of obtaining a remission is to give soluble corticotrophin in an intravenous infusion. In severe cases about 20 mg. in a

firms the impression that in severe cases which have not responded to traditional methods cortisone is perfectly legitimate therapy and may be beneficial. It is most effective as a temporary measure in an acute attack. It may also be useful if given in a series of courses, but is no better than standard methods when used continuously. A cheap and

more traditional methods.

they are effective in suppressing symptoms Hydrocortisone snuff is said to give excellent results.

(iii) **Pulmonary Sarcoidosis.** Where this disease causes distressing symptoms or where it fails to clear itself spontaneously after a few months, the use of steroids seems indicated. These drugs induce a

which took place during this period were also less frequent in the

extremely effective method of treating this condition is with hydrocortisone retention enemata or rectal infusions.

(ii) **Sprue and Coeliac Disease.** In severe and resistant cases of both

appetite ersists
despite The
aim in of the

will rapidly reverse the severe metabolic anomalies, and their resulting symptomatology, in cases of acute hepatitis and even in some cases of hepatic coma. In chronic hepatitis on the other hand, the most that can be expected from steroid therapy is a slight degree of symptomatic improvement.

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of the
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diagnosis.

C. Respiratory Diseases

(i) Asthma.

the fact that they are not usually on the drug for long enough to get a complete adreno-cortical suppression.

If one conscientiously treats and retreats all the relapses as they occur, one may expect to get a permanent remission rate of about 40 per cent. in any representative series.

E. Ophthalmological Diseases

Cortisone and corticotrophin have a definite but limited role in ophthalmological disorders Their effect is limited to the control of inflammation and exudation. As in the other diseases we have dis- [illegible]

essential.

[illegible]

tuberculous.

The principal ophthalmological complications of the rheumatic diseases are: iridocyclitis, scleromalacia perforans, keratoconjunctivitis sicca (Sjogren's syndrome), and episcleritis Of these, the first responds excellently [illegible]
are not impr [illegible]
out any hope [illegible]
basis alone. [illegible]
is exception [illegible]

F. Endocrine Diseases

In this group of disorders, cortisone and corticotrophin are frequently used for their *physiological* as opposed to their *pharmacological* properties. Thus, for example: In *Addison's disease*, cortisone has largely supplanted desoxycortone in treatment. Doses varying between

to the duration for which the disease has been present The side-effects are similar to those in all the other diseases which have been discussed, but they may occur more frequently, as in many cases a maintenance dose of over 100 mg. a day is necessary to control the symptoms and signs. It will be remembered that this disease figured in the " Obligatory List " issued by the Ministry of Health in 1954. [illegible] ily men- [illegible] was no [illegible] several recorded cases in the literature in which extremely satisfactory control has been established with cortisone and even more so with corticotrophin.

D. Renal Diseases

Renal function is to some extent under the control of the hormones of the suprarenals, and the kidney's excretory function is stimulated by the administration of cortisone. The ability of the diseased kidney to respond to such a stimulus is variable and the increase in function may be more than counterbalanced by the extra load placed on the kidney by the catabolic effects of the hormones.

Therefore under the influence of cortisone a patient with renal disease *may* manifest increased proteinuria, œdema and hypertension. However in general these are temporary phenomena which disappear as soon as the drug is stopped.

In practice, steroid therapy is contra-indicated in the presence of significant renal insufficiency or uræmia. It has a beneficial effect in most types of *nephrotic syndrome*, but not in the Kimmelstiel-Wilson type of diabetic nephrosis.

There is little doubt that these drugs have significantly improved the prognosis of adult forms of nephrosis and probably also of the juvenile forms.

No set plan of dosage has been established, nor is the mode of action of the therapy clearly understood. There is often an initial worsening [illegible] the serum protein levels

As soon as the administration of cortisone is cut, there is usually a very profound diuresis which occasionally continues until the elimina- [illegible] infection.

This is one of the only conditions in the whole of medicine where the sudden withdrawal of cortisone is not reprehensible. Indeed it is actually indicated as we wish to make use of the adrenal rebound effect. That the patients do not come to any serious harm is probably due to

the fact that they are not usually on the drug for long enough to get a complete adreno-cortical suppression.

If one conscientiously treats and retreats all the relapses as they occur, one may expect to get a permanent remission rate of about 40 per cent. in any representative series.

E. Ophthalmological Diseases

Cortisone and corticotrophin have a definite but limited role in ophthalmological disorders. Their effect is limited to the control of inflammation and exudation. As in the other diseases we have discussed, their exact mode of action is unknown but they seem to act by suppressing the reaction of the tissues to various insults, and not on the primary cause of the disease.

In diseases of the external eye and of the anterior ocular segment, it is preferable to use a topical application of cortisone or hydrocortisone, either in the form of an ointment or as eye drops. Both of these are available in strengths ranging from 0·5–2 5 per cent. However in diseases of the posterior ocular segment, the systemic use of the drugs is essential.

[illegible]

[illegible]

associated with vitreous opacities, they may literally be a sight-saving measure, provided that one can be sure that the ætiology is not tuberculous

The principal ophthalmological complications of the rheumatic diseases are iridocyclitis, scleromalacia perforans, keratoconjunc- [illegible]

F. Endocrine Diseases

In this group of disorders, cortisone and corticotrophin are frequently used for their *physiological* as opposed to their *pharmacological* properties. Thus, for example: In *Addison's disease*, cortisone has largely supplanted desoxycortone in treatment. Doses varying between

12·5 and 37·5 mg./day by mouth maintain many patients in perfect health. However a few will require the implantation of a small dose of desoxycortone acetate as well in order to keep up the blood-pressure. Any significant form of stress such as an intercurrent infection or an operation necessitates the raising of the cortisone dosage up to levels of about 100 mg. per day. When the stress is over, the dose should be gradually decreased.

An *Addisonian crisis* requires an immediate intravenous infusion of [illegible]

adrenal responsiveness.

The Waterhouse-Friderichsen Syndrome was almost uniformly fatal before the advent of intravenous preparations of hydrocortisone. Nowadays, provided that a sufficiently early diagnosis is made, sub- [illegible]

the Westminster Hospital consists of three doses of 100 mg. intramuscular cortisone given forty-eight, twenty-four hours, and one hour before the operation. After the operation, a similar dose is injected every six hours for twenty-four hours, then twice on the next day. Oral cortisone is then given for two days in doses of 25 mg. every six hours. [illegible] reduced by [illegible] *dose which* [illegible] *tomy*, small doses of cortisone, in conjunction with other essential hormones, are required indefinitely.

[illegible] the presence of a recognized stress [illegible]

corticotrophin from the pituitary as does hydrocortisone, and this sets up a vicious circle by stimulating the further production of adrenal androgens.

The administration of cortisone to such a patient, seems to break this vicious circle by suppressing corticotrophin production by means of the "feed-back" mechanism discussed elsewhere. The output of adrenal androgens falls correspondingly and normal female sexual characteristics are enabled to develop to some extent.

The aim in treating this condition, is to reduce the 17-ketosteroid secretion in the urine to normal levels. For this purpose it has been suggested that intramuscular injections of cortisone provide a more steady blood-level than oral administration. Wilkins, who originally described this particular form of treatment, recommended an injection of 75 mg. cortisone every third day. More recently, however, there has

600–1,000 mg. once per month may be quite sufficient to control the disease.

Malignant exophthalmos, especially if early and acute, may respond to steroid therapy. ACTH is probably preferable to cortisone, and sodium restriction should be used to prevent local fluid accumulation. *Acute thyroiditis* has also been treated successfully.

G. Hæmatological Diseases

Once again we have to confess that the therapeutic indications are

taneous lymphopenia and eosinopenia. They also cause a measurable degree of erythropoiesis. Since none of these phenomena can logically be linked with various observed therapeutic effects, we have to fall back on rather vague hypotheses about the modification of antigen-antibody reactions to explain them.

Hæmolytic anæmias. There are only two groups of hæmolytic anæmias in which these drugs are consistently effective, they are the idiopathic acquired variety and "symptomatic" hæmolytic anæmias. They are quite ineffective in congenital acholuric jaundice, Cooley's anæmia, nocturnal hæmoglobinuria and sickle-cell anæmia.

In *idiopathic acquired hæmolytic anæmia* one occasionally finds patients

will respond satisfactorily. Cortisone may however be a life-saving measure.

By "*symptomatic*" *hæmolytic anæmias* we mean those cases in which the hæmolysis is secondary to some well-defined primary condition such as Hodgkin's disease or disseminated lupus erythematosus. The relief of the anæmia in this group seems to be in direct proportion to the susceptibility of the primary condition. Thus to revert to our examples, the anæmias associated with disseminated lupus are far more likely to respond favourably than those based on an underlying Hodgkin's disease. The improvement which usually occurs in the

can explain the improvement in the anæmia of certain cases of leukæmia when treated with cortisone by the same mechanism.

Idiopathic thrombocytopænic purpura. This is the second condition in which steroid therapy may occasionally provoke an apparent cure In most other cases it constitutes an excellent form of treatment. A

by no means constant, and its extent does not correlate well with the

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well worth trying in patients who develop purpura secondary to drug sensitization.

is in some degree specific and fortunately does not interfere with the expected response to folic acid antagonists or 6-mercaptopurine. Conversely, resistance to these anti-leukæmic drugs, which almost

always develops after a time, does not imply necessarily a resistance to the steroid drugs.

One obvious deduction from this seems to be that both forms of

revert towards normal. The remission may last a few weeks or a few months. In very rare case it lasts up to a year. Then gradually, despite a progressively augmented maintenance dose, the condition will relapse and the leukæmic peripheral blood and bone marrow picture will return.

It is impossible to predict on an individual basis which case of leukæmia will respond and which will be resistant. In general terms, however, we can say that children usually respond better than adults, that acute leukæmias respond better than chronic, and that lymphoblastic leukæmias respond better than the myeloblastic types. In a

cent. of adults treated with cortisone

The same author points out that whilst, in general, one cannot say

disappointing though these may also be.

H. Miscellaneous Conditions

(i) **Burns.** During the Korean war a series of very encouraging

be performed, and this hastened the entire recovery process.

It is difficult to understand how reports of this nature could have been erroneous, since one would have thought that, unlike that of the other conditions which we have discussed, the assessment of therapy in burns would have been a matter of simple observation. However, subsequent experience has been very disappointing and many surgeons do not recommend it at all.

will respond satisfactorily. Cortisone may however be a life-saving measure.

By "*symptomatic*" *hæmolytic anæmias* we mean those cases in which the hæmolysis is secondary to some well-defined primary condition [illegible]
The [illegible]
to [illegible]
examples, the anæmias associated with disseminated lupus are far more likely to respond favourably than those based on an underlying Hodgkin's disease. The improvement which usually occurs in the [illegible]

can explain the improvement in the anæmia of certain cases of leukæmia when treated with cortisone by the same mechanism.

Idiopathic thrombocytopænic purpura. This is the second condition [illegible]

response includes a return of the platelets to normal. However, this is by no means constant, and its extent does not correlate well with the degree of clinical response.

If the remission is not maintained when the drugs are withdrawn, a decision has to be made about the advisability of splenectomy. Unfortunately the effectiveness of this operation seems to bear no relationship to the response of the platelets to cortisone As a result one has virtually to guess in each case how much benefit will be achieved by it. It is not at all unknown for the patient to have to continue taking cortisone permanently following an unsatisfactory splenectomy.

Allergic purpura, such as the Henoch-Schonlein type. One frequently gets an excellent response from steroid therapy; it is also well worth trying in patients who develop purpura secondary to drug sensitization. Where the purpura forms part of a general bone marrow dysplasia, the prognosis naturally is that of the primary condition.

Agranulocytosis. It is sometimes difficult to be sure whether the [illegible]

complementary to each other and that every case in which there is no [illegible]

is in some degree specific and fortunately does not interfere with the expected response to folic acid antagonists or 6-mercaptopurine. Conversely, resistance to these anti-leukæmic drugs, which almost

occurring in pregnancy. There have been a number of conflicting reports of the use of steroids in *disseminated sclerosis*. The effects of any treatment are notoriously difficult to assess in a disease which is subject to spontaneous remissions, but steroids may be worth a trial in early cases or in patients who have had a prolonged relapse.

To end on a non-medical and rather more flippant note we must record that the steroid drugs have found an undisputed, if illegal, use in the hands of racehorse and greyhound trainers who discovered that it increases both the speed and the endurance of their charges It is not immediately clear which physiological action is being invoked for this " sporting " purpose, but it seems a little ironical in view of the persistent controversy about the indications and justification for these drugs in medicine, that there is no argument whatsoever as to their potentialities amongst the bookmaking fraternity.

In the only case in which the author has been concerned, there was general agreement between the surgeons and the nursing staff that the child had suffered very much less shock than would have been expected on the basis of previous experience. The healing process was also rapid and uneventful.

In a recent review it is pointed out that cortisone is a more logical

authors make the point that it should probably not be given in any case for longer than three days at a time for fear of encouraging the spread of infection As the cortisone is withdrawn, they recommend that it is temporarily replaced by corticotrophin so that the adrenal is not left suppressed during the period of crisis. These authors go on to say that cortisone can frequently be employed very usefully between the third and the tenth weeks. At this stage, it may assist a recalcitrant skin graft to take.

(ii) **Tuberculosis.** Cortisone is being used more and more in the treatment of tuberculous infections, and it is now not uncommon to combine it with antibiotics in the treatment of pulmonary tuberculosis for example. This is at first sight a startling development in view of the early scares about using cortisone if there was any possibility of a tuberculous lesion ever having been present. The rationale of course is that cortisone by its effect on connective tissues enables the antibiotics to gain access to organisms which have settled in avascular and fibrotic tissue Animal studies have shown that tubercle bacilli are disposed of just as rapidly, even though the inflammatory reaction is suppressed.

Indications for the use of cortisone include obstructive lesions due to adhesions, hypersensitivity, and to cover any stress such as a major operation It is still not decided whether patients with cavities should be treated with these drugs

(iii) **Trichinosis.** Cortisone is said to give marked symptomatic relief in this disease. The fever, œdema and muscular pains disappear rapidly and the percentage of circulating eosinophils is substantially diminished.

(iv) **Neoplasia.** In general, these drugs have no beneficial effects in

... that in these carcinomata

benefit ...

maintenance therapy with cortisone.

(v) ... conditions. Favourable results have been reported

... should be pointed out that this

... While of no benefit in *chorea,*

cortisone may be valuable in the more severe forms of the disease

We have discussed in our introductory pages the striking contrast in the effect between European and American experiences which resulted from these distribution and production problems There is no doubt that its later and more gradual acquisition in this country enabled us to profit from some of the unfortunate experiences suffered by many of

and to return to their original high dosage at any price. These people spent the rest of their lives precariously perched between the states of drug dependency and economic destitution.

Thus in this one short section, we have purposely contrasted the unique example of the help given by commerce in overcoming production problems with the dreadful harm for which other commercial forces must be held responsible. There is no doubt that they encouraged premature distribution and excessive publicity on an unprepared public and medical profession

World Opinion and Therapeutic Trials

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publicity.

In the early days our major problem consisted of trying to select the

volunteers who

was a feat re-

hen both these

qualities were used in full measure, one was frequently made to feel

meaning friends and fellow-patients are certain to regale them. It is not at all uncommon for such patients to return for their first follow-up visit with their supply of cortisone untouched because they are too scared to take it! Even worse was the patient who had been

CHAPTER 7

GENERAL DISCUSSION

We have still left unanswered some of the pertinent questions to which we committed ourselves at the outset of this book. We aim in this final chapter to roam provocatively in these uncharted regions trying to evaluate the general significance of Hench's discovery in the light of eight years' experience.

We shall discuss these problems under the following headings:

(i) Production problems.
(ii) World opinions and therapeutic trials.
(iii) Personal opinion
(iv) The impact of cortisone on clinical rheumatology.
(v) The mode of action of cortisone. A. Original hypothesis. B. Subsequent theories.
(vi) Prospects for the future.

Production Problems

That we should choose to start our general discussion with this topic is a measure of the vital, but too often forgotten, part which it has played in the development of our theme.

In 1949, the manufacturing chemists were uniformly gloomy about [illegible] would not have made any impact on the problem with the methods of extraction and synthesis which were available at that time.

[illegible]

It involved the close co-operation and pooling of ideas by chemists, botanists, biologists, physicists and engineers, and it is a supreme example of the interdependence of science and industry in overcoming formidable obstacles.

In spite of all this, cortisone remains a comparatively expensive drug, and on this count alone it can only justify its use if it can contribute to the patient's welfare something which cannot be obtained more cheaply.

in retrospect—that our tacit acceptance of this state of affairs was justified in the light of the limited knowledge available

carefully planned trials

In the case of cortisone, there were other unusual problems which made controlled work exceptionally difficult, even when tablets took

were totally irrelevant when it came to evaluating powerful anti-inflammatory drugs such as cortisone. Consequently we had to start from the beginning to devise new clinical tests which were more appropriate to the new circumstances

Cortisone-Aspirin Trials

anatomical changes in the joints or by the systemic sequelæ of a prolonged and debilitating illness. Six centres in England and Scotland took part, and the criteria of patients for inclusion in the trial were (*a*) ages 2 to 59 years inclusive (*b*) a polyarthritis of rheumatoid type affecting at least four joints and bilateral involvement of either hands or feet, ankles or wrists, and (*c*) duration of disease not less than three or more than nine months Measures were taken to ensure that the cortisone and aspirin groups would be very similar in sex, age, duration of illness and treatment centre. Of the 61 adult patients included in the trial 30 were on cortisone and 31 on aspirin An assessment at the end of the first year of treatment showed that in both groups the disease ran a closely parallel course in nearly all the recorded characteristics—namely joint tenderness, range of movement in wrist, strength of grip, tests of dexterity of hand and foot, and clinical judgment of the activity of the disease and the patient's functional capacity The hæmoglobin level and blood sedimentation rate were slightly more favourably influenced by cortisone. At the end of the second and third year's of observation there was observed no difference outside the limits of chance, and it was concluded that for practical purposes there was remarkably little to choose between cortisone and aspirin in the management of this particular group of patients with Rheumatoid disease of recent onset.

A later trial organized by the Empire Rheumatism Council included a wider variety of patients in both the severity and duration of their arthritis The results of the second year of this trial have now been

on the drug for some time and who overheard a conversation between two " connoisseurs "
She cut her maintenar
and without askingan
in on a stretcher having suffered the most severe rebound relapse, which took several weeks of in-patient treatment to reverse.

It is only too easy to indict the lay press for this state of affairs, but we as a profession must take a very considerable share of the blame To put it bluntly, we were caught unprepared by the speed of events following Hench's discovery; we had neither the knowledge nor the facilities in many cases to evaluate such a revolutionary type of drug.

The author has recently had occasion to collect and study 51 of the early clinical reports describing the results of long-term cortisone therapy in patients suffering from rheumatoid arthritis. Almost without exception these reports were grossly inadequate and confused in the data they supplied and, with two notable exceptions, not one of them was adequately controlled by a similar group of patients receiving placebo or orthodox therapy. We, who were just as culpable on this score as the majority, find it interesting to reflect back to those exciting days and try to recall the motives for our apparent negligence.

It must be remembered that there was a delay of about nine months between the original fanfare announcing the discovery of cortisone, and the arrival of the first official supplies for clinical trials in this country These were frustrating and impatient months for us; and when the allocation finally arrived we found that it was only sufficient to treat five patients for ten days each.

This short-term study was carried out with stringent controls, and

compared

Furthermore our control cases began to sense that they were not responding in the same way as their colleagues and gradually they began to drift away from our care By contrast, the cortisone-treated cases have remained steadfastly faithful and even today, six years later, we still see the majority of them in routine follow-up clinics established for the purpose.

Personal Opinion

Having quoted from these authoritative sources, we cannot shirk the responsibility of declaring our own opinion as to the ultimate status of this group of drugs in rheumatoid arthritis.

We believe that cortisone, or one of its analogues, is *strongly* indicated in about 10 per cent of all the routine cases of rheumatoid

arrived at a state of permanent crippledom long before the drugs were discovered, so that a higher percentage of our patients will fall into the

ahead about fifteen years.

The Impact of Cortisone on Clinical Rheumatology

Whilst the ultimate fate of these drugs as practical therapeutic agents remains in the balance, there can be no uncertainty when we come to consider their significance in the spheres of medical research In the specialist field of rheumatology the effect has naturally been even more striking.

In 1949 this group of diseases was still considered one of the Cinderellas of the medical sciences, chronically short of funds and facilities, and conspicuously lacking the " back-room boys ", who are essential to the progress of any clinical discipline.

The early workers in the subject had done invaluable work by their careful observations, descriptions and classifications, but by 1949 these approaches were played out and they urgently needed the stimulus of a new concept in order to develop their observations.

Hench's discovery transformed rheumatology overnight from its Cinderella status. It has resulted in a considerable influx of new blood into the speciality and, of necessity, a profound broadening of the interests of existing rheumatologists. Their successful efforts to master the metabolic and endocrinological implications were extremely impressive. Many of them even managed to acquire a good working knowledge of steroid biochemistry This became essential in order to plan co-operative research with their new colleagues The diffusion of

published on 70 of the 99 patients originally selected for observation. Of these 36 were on cortisone and 34 on aspirin. Most of the withdrawals were for serious side effects and it is stated that they did not bias the relative composition of the groups in any defined way Again, no statistically significant difference could be demonstrated between the two groups as regards their functional capacity, number of joints affected, sedimentation rate or hæmoglobin. The x-ray appearances deteriorated in both groups but to a slightly greater extent in the aspirin than in the cortisone group as judged by the appearances of the hands. But the differences were only just significant over the whole two year period.

These two trials and the untoward effects which have followed cortisone therapy naturally evoked serious doubts about the wisdom of using cortisone in rheumatoid arthritis, and this was undoubtedly salutary in view of the earlier claims by unbridled enthusiasts, but so to interpret them would not necessarily be valid. The results do not exclude the possibility that individual patients, unpredictable in the light of our present knowledge, may show greater benefit from cortisone than from other forms of treatment, though the latter must not be neglected.

Cortisone-Prednisone Trial

As an encouraging contrast to these negative results a preliminary report was published in July, 1957, of a further multicentre controlled trial carried out by a joint committee of the Medical Research Council and Nuffield Foundation in which a comparison was made between the relative effectiveness of Prednisone and Cortisone in the treatment of Rheumatoid Arthritis.

Sixty-eight patients have so far been assessed over a period of one year Of these 35, who were selected at random, had their therapy changed from cortisone to the new derivative. At the end of one year the cortisone group showed no material change for better or worse, whereas the prednisone group showed improvement in the strength of grip, blood sedimentation rate, hæmoglobin level, functional capacity and disease activity. In five patients on prednisone the disease was judged to be inactive but this did not occur at all in the cortisone group.

The relative benefits were seen most clearly in the first three months after the switch to prednisone but it is suggested that the failure to maintain the improvement may have been partly due to the progressive reduction is dosage in the course of the year.

The incidence of "moon facing" was noted to be much higher in the prednisone group and the committee cautiously suggest therefore that the more favourable results observed with prednisone might, in part, have been due to a dosage which was relatively high in comparison to the dosage of cortisone This certainly seems a possible [illegible]

of prednisone.

being energetically tackled on both sides of the Atlantic. It seems

altered by disease and also by cortisone

which we, as clinicians, are so often confronted It is however unproven, and there are several substantial objections to its total acceptance.

The danger which it holds by virtue of its simplicity and plausibility is that it may dull our clinical faculties and our attempts to observe, record and classify our cases in the classical manner.

This would be an unwarrantably retrogressive step, since clinical

hypothesis is proven beyond any possible doubt.

When this has occurred in our present context it may be that the sphynx-like rheumatic diseases will have yielded up their fundamental secrets at last.

We may optimistically hope that this will occur in our generation, but we must constantly remember that the chink in their defences is so far infinitesimally small. Until it does occur we feel that "the splitters'" approach to rheumatology has more to commend it than "the lumpers'".

The Mode of Action of Cortisone

A ORIGINAL HYPOTHESIS

" What physiological processes are modified by cortisone and how the influence is exerted, are matters still locked within the hormones of the adrenal cortex" (Kendall, 1950)

We have now arrived at what is known in American vernacular as "the sixty-four-dollar question". We have in all humility recorded in the earlier sections of this book a series of problems which have so far baffled us in relation to this new group of drugs. The question of how they work is not only the most fundamental but also the most frus-

it would have seemed inconceivable at that time that we should still be floundering for an explanation in 1957 with considerably less confidence than we felt in 1950.

new knowledge and new personalities into and out of a speciality in this way is a sure guarantee of its health for years to come

In addition to this, cortisone provided dramatic proof that Hench's doctrine of "potential reversibility" was a very real phenomenon and not just a catch-phrase. It immediately elevated the criteria used in assessing therapeutic results to an extent which would have seemed ludicrous previously.

Another very challenging problem arose because of the wide therapeutic spectrum of this group of drugs. Several diseases presenting completely different clinical pictures seemed to respond equally well. From this observation, two schools of thought developed which have been facetiously described as "the splitters" and "the lumpers". The former continued to classify the different syndromes as if they were all disease entities in their own right, each one probably having its own specific ætiological factors.

The latter argued that these different clinical pictures all arose from a basic abnormality of the connective tissues and that the differences between them could be explained in terms of the distribution of the lesions within the body. Thus they might be predominantly skeletal as in rheumatoid arthritis and ankylosing spondylitis. In others there might be an imperceptible merging into diseases like diffuse lupus erythematosus, where the predominant, but pathologically similar, lesions are widely disseminated in the viscera, scleroderma, where the connective tissues of the skin bear the brunt of the changes; or dermato-

ɔt that connective
ɔm a pathological
point of view to a large number of potential insults. Any one of these can act as a trigger factor stimulating a hypothetical chain reaction of events which give rise to the different clinical pictures. The basic response of the connective tissues in these diseases is known as "fibrinoid necrosis"

by this ingenious hypothesis were appreciated

Whether time proves "the lumpers" or "the splitters" ultimately

Once our attention was thus focused, our profound ignorance of the structure, chemistry and metabolism of these tissues became all too apparent. However the advent of new techniques such as electron

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rmal
ground substance, let alone pathological changes. But the problem is

being energetically tackled on both sides of the Atlantic. It seems possible that these studies will prove to be fundamental to our understanding of the rheumatic diseases and that once the chemistry of the normal is known it will not be long before the abnormalities of diseased tissue are classified. When we are in a position to do this we may hope to find out if, and by what mechanism, its molecular configuration is

ig would not be amiss

" is attractive, and it certainly helps to explain many of the puzzling mixed syndromes with which we, as clinicians, are so often confronted. It is however unproven, and there are several substantial objections to its total acceptance.

The danger which it holds by virtue of its simplicity and plausibility is that it may dull our clinical faculties and our attempts to observe, record and classify our cases in the classical manner.

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We explained in our introductory chapter the logical and imaginative sequence of observations and interpretations which led Hench to try his initial experiment in 1948. It must be unusual in the history of therapeutics for such a triumph of reasoning to prove so successful in practice and yet to have its underlying hypothesis swept away by later developments

To recapitulate: Hench, because of his careful observations on pregnancy and jaundice remissions, was searching for the hypothetical "anti-rheumatic substance *X*" In the course of his researches he noted the anti-inflammatory clinical effects of cortisone. One of the [illegible]

failure of supply or to an unexplained excessive demand. The latter might possibly have been due to a state of idiopathic resistance in the affected tissues. In pregnancy, it was said that the natural production of adrenocortical hormones was increased, and in hepatitis, their breakdown by the liver was said to be decreased.

These theories, although superficially attractive, have little or no experimental evidence to support them, indeed there is considerable evidence to the contrary.

For example, Hench himself recorded in 1954 that the corticosteroid excretion of the rheumatoid arthritic patients attending his clinic was within normal limits (0 3–1·2 mg./24 hours) and that they responded quite normally to injections of corticotrophin. We found that only four of our cases had subnormal excretion levels. Selye attempted to [illegible]

responsible for the imbalance.

There is, however, little or no evidence that such an imbalance occurs in rheumatoid arthritis, and a recent clinical experiment carried out at Guy's Hospital, in which it was attempted to influence the rheumatoid state by varying the ratio of administered gluco-corticoids and mineralo-corticoids, gave entirely negative results

The theory of excessive tissue demands or tissue resistance in these patients has also proved to be a sterile field for research so far, since by all the techniques available no consistent differences have been found in vitro between rheumatoid and normal connective tissue. It is quite possible that these results are due to our technical limitations and that future research may reveal facts which are too subtle for present methods.

[illegible]

remission is not so direct as it appeared. By contrast, it is only recently that evidence has been obtained in the United States that there is a consistently raised level of circulating corticoids in jaundice.

B SUBSEQUENT THEORIES

It would seem therefore that we are forced to modify some of Hench's original theories, and the problem of how pregnancy and jaundice cause a remission remains a fascinating challenge for future workers. In trying to fill the resulting gap in our knowledge we are forced to improvise theories based on the known pharmacological action of these drugs

ment, and there is still considerable disagreement on points of interpretation. Most authorities agree that the nodules are significantly

element.

largely virgin research territory, but there is some evidence that cortisone increases the degree of polymerization of hyaluronic acid, and it is conceivable that this may be important from a therapeutic point of view It is probably responsible for the increase in the viscosity of the synovial fluid which is a constant clinical finding

(c) Effect on Capillary Permeability. It was demonstrated as early as 1950 by Robson and Duthie in Edinburgh, that cortisone has a very marked effect on capillary permeability. Other workers have confirmed this finding and have noted that whatever method was used to provoke inflammation, the capillary response was the same and appeared to consist of a maintenance of vascular tone, reduction of damage to arteriolar and venular epithelium, and, as a direct result of its effect on the integrity of vascular endothelium, a decrease of cellular and humoral exudation. As soon as the cortisone was withdrawn the inflammatory state returned.

Several workers have confirmed that cortisone has a specific inhibitory action on the leucotactic peptides, which are released in response to such insults, and one of them has claimed to demonstrate

[illegible] imaginative sequence [illegible] to try his initial experiment in [illegible] [illegible]tory of therapeutics for such a triumph of reasoning [illegible] [illegible]ssful in practice and yet to have its underlying hypothesis swept away by later developments

To recapitulate: Hench, because of his careful observations on pregnancy and jaundice remissions, was searching for the hypothetical "anti-rheumatic substance *X*". In the course of his researches he noted the anti-inflammatory clinical effects of cortisone. One of the many reasonable interpretations of this phenomenon was that certain diseases were caused by an unsatisfied tissue demand for these hormones.

The deficiency, it was postulated, could either have been due to a failure of supply or to an unexplained excessive demand. The latter might possibly have been due to a state of idiopathic resistance in the affected tissues In pregnancy, it was said that the natural production of adrenocortical hormones was increased, and in hepatitis, their breakdown by the liver was said to be decreased

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There is, however, little or no evidence that such an imbalance occurs in rheumatoid arthritis, and a recent clinical experiment carried out at Guy's Hospital, in which it was attempted to influence the rheumatoid state by varying the ratio of administered gluco-corticoids and mineralo-corticoids, gave entirely negative results

The theory of excessive tissue demands or tissue resistance in these patients has also proved to be a sterile field for research so far, since by all the techniques available no consistent differences have been found in vitro between rheumatoid and normal connective tissue It is quite possible that these results are due to our technical limitations and that future research may reveal facts which are too subtle for present methods

Finally, we have seen cases in whom the disease became worse during each of several pregnancies and yet was fully sensitive subsequently to cortisone therapy. This suggests that the apparently simple relationship between pregnancy, increased circulating corticosteroids and disease remission is not so direct as it appeared By contrast, it is only recently that evidence has been obtained in the United States that there is a consistently raised level of circulating corticoids in jaundice.

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We know of no adequately controlled trials in which the effect of

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Conclusion. From these varied observations, it seems certain that the anti-rheumatic activity of cortisone is due to a local, non-

phenomena.

Thorn and his colleagues, in a series of excellent review articles, concluded that the diverse and non-specific action of the adrenal steroids indicated a single fundamental action at the cellular level, and it may be that their action on cellular permeability will eventually prove to be the one common denominator by which they produce their clinical effect

question"

Prospects for the Future and Conclusions

We have now completed our survey of the historical and practical aspects of steroid therapy in rheumatology and general medicine as they exist today It remains for us to try to evaluate the probable verdict of posterity on this discovery Only in this way can we hope to retain a sense of perspective and to appreciate the many and important lessons which we have learned from eight years of experience

Let us therefore try to project ourselves forward in imagination about fifty years and hazard a guess as to how our subject will be reported in a textbook of that era

Our first and confident guess is that the patient clinical research which led Hench to his discovery will still be regarded as amongst the epoch-making investigations in the history of medicine and that its author is assured a permanent place amongst the immortals

that cortisone is able to accumulate in just those areas in which inflammation is taking place.

There is no doubt that this capillary effect must be anti-inflammatory and the fact that the drug is said to accumulate mainly in the inflamed tissues may partially explain its beneficial action in arthritic joints and rheumatoid nodules

(*d*) **Effect on Enzyme Systems.** Here again our knowledge is largely embryonic, and we only mention it here because we believe that it is likely to prove a fertile field of research which will yield important results as techniques develop. It is not at all improbable that the metabolism of the connective tissues is determined by subtle enzymatic control, and there is some evidence that cortisone can modify several of these enzymatic processes.

(*e*) **Inhibition of Fibroblastic Activity.** This has already been discussed in relation to the inhibition of wound healing It is certainly a marked phenomenon in experimental animals, but there does appear to be some species specificity This, combined with the relatively higher doses given to animals, on a weight for weight basis, makes it difficult to evaluate its importance in a clinical context. Not only are the fibroblast precursors inhibited, but there is also an inhibition of capillary proliferation, so that the amount of granulation tissue which develops is considerably less than normal By contrast, epithelial regeneration is quite normal These actions are naturally of potential importance when considering a chronic inflammation such as occurs in rheumatoid arthritis

(*f*) **Inhibition of the Production of Chondroitin sulphate and Collagen.** There is experimental evidence for both these phenomena. The inhibition of the production of metachromatic materials such as chondroitin sulphate is said to be related to a reduction in the number of mast cells in the connective tissue. The inhibition of collagen has been observed in tissue culture work and has been confirmed biochemically Again it is difficult to evaluate the clinical significance of these but they are at least potentially relevant in diseases in which the main brunt of the disease falls on the connective tissues.

(*g*) **Allergic and Anaphylactic Phenomena.** There is considerable evidence that cortisone can suppress or abolish most of the experimental anaphylactic reactions. For example it can inhibit both the Schwartzman and the Arthus phenomenon It also inhibits the response to tuberculin injections in sensitized subjects As a corollary to this, a marked diminution in circulating antibodies has been demonstrated in patients receiving cortisone This is probably due to a suppression of antibody synthesis By contrast, cortisone has no direct antihistamine effect

These observations are specifically stressed in this review since there is a growing and independent body of medical opinion which considers that the inflammatory responses seen in rheumatoid arthritis are in the nature of an allergic response to some undefined allergen. It could be at this point that the action of cortisone approaches most nearly to the ætiology of the diseases in which it is effective.

(*h*) **Anti-Hyaluronidase Action.** Here again the clinical significance

APPENDIX I

THE ANATOMY AND TECHNIQUE OF INTRA-ARTICULAR AND SOFT TISSUE INJECTIONS

By J. G. Bearn, M B , B.S.

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The following principles should be kept in mind.

For intra-articular injection

1. The site should be as far removed as possible from nerves and blood vessels.

2. The site should be indicated by bony landmarks, these being more r

3.

ing, ar

avoided.

4. In general the extensor surface of the joint is usually the ideal site for the injection, the joint cavity being closer to the skin, and more remote from blood vessels and nerves

For soft tissue injection

1. The site of the lesion should be determined by conventional diagnostic measures. Detailed localization demands the co-operation of the patient, who can sometimes pinpoint the affected area accurately

2. Pain is frequently noticed when the needle point reaches the site of the lesion To avoid confusing this pain with cutaneous pain, skin anæsthesia should be used.

3. When injecting tendon sheaths the needle should be inserted obliquely as in venepuncture and a palpating finger proximal to the site of injection will feel the fluid running up the sheath In superficial

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Multiple

skin pricks may have to be made to cover the area, but as a rule these diffuse injections are not very satisfactory A useful practical procedure in such cases is to infiltrate the area with procaine and only to inject hydrocortisone if the area of tenderness can be abolished by the local anæsthetic

Needles

The following needles have been found suitable for injections. If aspiration is required, a larger bore needle is more convenient.

secure foundations, the next few years will show a considerable expansion of our basic research activities, using techniques which were undreamed of in 1949.

Along with new techniques, an army of scientific workers have interested themselves in the field of rheumatology and the results of their endeavours will inevitably become clear in the foreseeable future. Patience is manifestly required while they are applying these techniques to the investigation of undiseased structures, this being an essential prelude to their application in disease states.

It would not be fanciful to attribute this renaissance of scientific interest in the rheumatic diseases almost entirely to the discovery of cortisone, and in retrospect this may be considered the most important single result of Hench's researches.

We should not expect rapid developments in the clinical field. We have, so to speak, temporarily thrown the ball back to the research workers and the clinician's present function should be essentially that of a co-ordinator and stimulator of their efforts.

Undoubtedly newer and more powerful steroids will be discovered from time to time, and already a set pattern in these discoveries is discernible. At the time of going to press we hear of clinical trials with 9-alpha-fluoro-delta-derivatives, in which the extreme potency of [illegible]

apparently still possesses the powerful salt retaining properties of the original 9-alpha-flouro compound.

We have also recently learned of the logical use of delta-hydrocortisone tertiary butyl acetate intra-articularly.

We have paid lip-service in the course of this book to the conception of the "ideal" steroid, i.e., one whose action is entirely anti-inflammatory, and in which all the dangerous side-effects have been overcome. This is theoretically quite possible, although there seem no prospects of it being discovered, except by chance, in the near future.

What we, as clinicians, have learned, and must remember, as a result of the last seven years, is a more critical approach in therapeutic assessments. We were caught largely unprepared by the impact of Hench's

tendon into the greater tuberosity of the humerus The bursa does not communicate with the shoulder joint normally. However, if the supraspinatus tendon has degenerated or ruptured, the bursa communicates with the joint through the defect in the tendon.

Position

The patient should be sitting on a stool with the arm hanging by the side.

Method

The lateral border of the acromion process is easily palpated on the lateral aspect of the shoulder

The needle is inserted horizontally in the lateral plane of the body just below the acromion.

The bursa is entered at a depth of about 1½ to 2 cm. If the needle is now inserted a further 2 cm. the supraspinatus tendon is pierced and the shoulder joint entered.

The shoulder joint (See Fig 1)

The shoulder joint may be injected from the lateral, posterior, or anterior aspect.

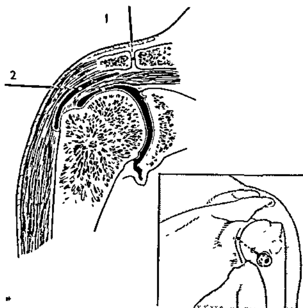


Fig. 1. Shoulder Joint.

1. Acromio-clavicular joint
2. Sub-acromial bursa, supraspinatus tendon and shoulder joint (lateral approach).

Inset Posterior approach to shoulder joint.

18 B.W.G. may be

but
oach

Knee joint
2-inch needle 20 or 22 B W.G.

Elbow, wrist, ankle and tarsal joints
1½-inch needle 22 B.W.G.

Finger and toe joints
1-inch 23 B W.G.

Soft tissue lesions
The length of the needle must vary with the depth of the lesion. A 1½-inch 22 B W.G will suffice for most cases.

Upper Limb

[illegible] of lesions which can occur in the region [illegible] rately [illegible]

Acromio-clavicular joint (See Fig. 1.)

Position

The patient is sitting in a chair with the arm hanging loosely by the side.

Method

The joint is readily palpated, the lateral end of the clavicle partially overriding the acromion

The needle is inserted directly through the superior aspect of capsule.

Sterno-clavicular joint

Position

The patient should be lying face upwards

Method

There is no difficulty in palpating the joint, since the medial end of the clavicle overrides the sternum.

The needle should be inserted directly into the joint through the anterior aspect of the capsule

It should be noted that the great vessels lie posterior to the joint.

Sub-acromial bursa (See Fig 1)

The bursa is deep to the upper part of the deltoid and extends under the acromion process. It overlies the insertion of the supraspinatus

Method

The lateral border of the acromion process should be identified first, and the superior aspect of the greater tuberosity is then palpated about ½ inch below its anterior end. Passive rotation of the humerus will facilitate recognition of the tuberosity, which will then be felt gliding under the palpating finger, and an area of tenderness may be found. The needle is then inserted directly into the tendon, or into the tender area, at a depth of about 1½ cm.

The long head of biceps

The long head of biceps is injected as it lies in the bicipital groove between the greater and lesser tuberosities.

Position

The patient should be lying supine with the arm to the side and the palm facing upwards, and the medial epicondyle of the humerus pointing directly medially.

Method

In this position the anterior aspect of the greater tuberosity may be palpated about ½ inch below the acromio-clavicular joint and in many patients the bicipital groove itself may be felt through the relaxed fibres of the deltoid, immediately medial to this

In those cases where the bicipital groove can be identified the tendon of biceps is injected directly, as it lies in the groove.

When the groove cannot be identified with certainty, the needle [illegible] region of the tendon.

The tendon of biceps

The tendon of biceps is inserted into the posterior aspect of the radial tuberosity, a bursa being present between the tendon and the anterior part of the tuberosity.

The insertion of the tendon is the usual site of the lesion.

Position

The patient is sitting with the arm resting on a table and the elbow flexed to 45 degrees

Method

The tendon is found in the cubital fossa, by supinating the forearm.

The needle is inserted lateral to the tendon, to avoid the brachial artery and median nerve lying medially and is directed along the line of the tendon to its insertion into the radius.

Tennis Elbow

The aim of the injection is to infiltrate the superficial extensor origin from the front of the lateral epicondyle of the humerus and the lower third of the lateral supracondylar ridge.

1. The Lateral Approach

This approach is identical to that for the sub-acromial bursa, the needle being inserted for a further 2 cm. through the supraspinatus tendon into the joint cavity.

2. The Posterior Approach

Position

The patient lies in the prone position with his arm by the side and internally rotated.

Method

The key to this approach is the angle of the acromion. This is the point where the lateral border of the acromion is continuous with the lower border of the crest of the spine of the scapula at an angle of about 90 degrees. It is easily palpated over the posterior aspect of the joint.

The needle is inserted about ½-inch below this point and is directed towards the tip of the coracoid process, i.e., anteriorly and about 10 degrees medially.

The needle passes through the posterior fibres of the deltoid muscle, and then the tendon of the infraspinatus, before piercing the capsule of the joint.

This approach has the great advantage that it avoids the axillary vessels and the brachial plexus.

3. The Anterior Approach

Position

The patient should be lying on a couch, with the trunk raised to about 60 degrees and the arm hanging loosely over the side

Method

The key to the anterior approach is the coracoid process. This is palpated through the relaxed anterior fibres of the deltoid, about ½ inch below the lateral third of the clavicle

The needle is inserted into the joint just below the tip of the coracoid and is directed anteriorly. It passes through the anterior fibres of the deltoid, the coraco-brachialis and the tendon of subscapularis

Care must be taken to avoid the cephalic vein in the delto-pectoral groove and the axillary artery and brachial plexus, which run medial to the coracoid process

This is a difficult approach in a very obese or muscular patient

Supraspinatus tendon (See Fig. 1.)

It should be noted that the insertion of the supraspinatus tendon into the superior aspect of the greater tuberosity of the humerus forms part of the floor of the sub-acromial bursa, and that a lesion of the supraspinatus tendon may involve the bursa itself

Position

The patient should be sitting upright on a stool with the arm hanging loosely by the side.

Wrist joint

This may be injected *dorsally* or *medially*.

DORSAL APPROACH

This may be distal to the head of the ulna or to the lower end of the radius.

Position

As for the inferior radio-ulnar joint.

Method I

The injection is made between the head of the ulna and the tri- [illegible]

The tendon of extensor carpi ulnaris is found and the needle is inserted directly into the joint, between the ulna and the triquetrum and on the radial side of the tendon.

Method II

Lister's tubercle at the lower end of the radius is first palpated, and then the joint line is found distal to the tubercle on the ulnar side of the radial extensor tendons. These may be made to stand out by getting the patient to clench his fingers.

The needle is then inserted straight into the joint between the radius and the lunate on the ulnar side of the radial extensors

MEDIAL APPROACH

The styloid process of the ulna is found The carpal bone distal to this is the triquetrum.

The tendon of extensor carpi ulnaris is found crossing the joint, and may be made to stand out by slight extension of the wrist. The needle is inserted just distal to the styloid process of the ulna anterior to the extensor tendon, directly into the joint.

De Quervain's Stenosing Teno-vaginitis

The lesion involves the tendons of abductor pollicis longus and extensor pollicis brevis, as they cross the lateral surface of the styloid process of the radius, under the extensor retinaculum. There may be tenderness and swelling present over the tendons as they cross the bone

The injection should be made directly into the tendon sheath, the needle passing obliquely as in venepuncture.

Carpo-metacarpal joint of the thumb

Position

The patient should be sitting with the arm resting on a side table.

Method

The joint is injected from its lateral aspect.

The abductor pollicis longus tendon, forming the lateral boundary of the "snuff box", is palpated and traced to the base of the first metacarpal. The joint line is then found anterior to this tendon, and is

Position

The patient should be seated and the arm resting on a side table, with the elbow flexed to 45 degrees and the thumb upwards.

Method

The lateral epicondyle is found, and must not be confused with the head of the radius just below, which may be recognized by pronating and supinating the forearm.

The tender area is identified in the region of the epicondyle, and is infiltrated directly.

The elbow joint

The injection is made through the postero-lateral aspect of the joint.

Position

The arm is positioned as for tennis elbow.

Method

The lateral epicondyle and the head of the radius are identified on the lateral aspect of the joint. The head will be felt rotating in the annular ligament when the forearm is pronated and supinated.

The joint line is then palpated between the posterior margin of the head of the radius and the back of the lateral epicondyle. The needle is inserted directly into the joint passing through the anconeus muscle and the posterior part of the capsule.

Golfer's elbow

The lesion is at the origin of the superficial flexors of the forearm from the front of the medial epicondyle

The medial epicondyle is identified and the needle inserted immediately anteriorly into the origin of the muscles, and the tender area infiltrated.

Note—The ulnar nerve lies posterior to the epicondyle.

The Inferior Radio-ulnar joint

This joint lies between the head of the ulna and the notch on the medial side of the lower end of the radius.

It is separated from the wrist joint by the triangular radio-ulnar disc, except when this, very occasionally, is perforated.

Position

The patient is sitting, with the arm resting on a side table, and palm facing downwards.

Method

[illegible] The head of the ulna is [illegible]

forearm. [illegible]

the capsu[illegible]

straight into the joint.

The needle is directed superiorly and medially towards the mid point of the inguinal ligament, and deflected about 10 degrees posteriorly.

The needle runs over the trochanteric line and hits the antero-inferior aspect of the head, where it will be in the joint cavity. If the needle is deflected too far posteriorly, it may stop short by striking the trochanteric line.

ANTERIOR APPROACH

Position

The patient lies supine.

Method

The femoral pulse is found just below the mid point of the inguinal ligament.

The needle is inserted about 2 inches lateral to this, and directed posteriorly and about 20 degrees medially. It pierces the anterior aspect of the joint, traversing the ilio-psoas muscle.

LATERAL APPROACH

Position

The patient lies on the good side with the good hip flexed and the other extended.

Method

The *upper* border of the greater trochanter is palpated through the insertions of the glutei (this must not be confused with the lower border which is much more easily found).

The needle is inserted about ½ inch above it and directed medially and about 20 degrees inferiorly. It passes through the superior part of the capsule and into the joint cavity at about the junction of the head and neck.

Knee joint. (See Fig. 3)

This joint is easy to inject and may be approached in a number of ways.

METHOD I

Position

The patient lies on a couch with the leg extended.

Method

The patella is palpated, and moved from side to side. The joint line is found between the lateral and medial side of the patella and the femur

The needle is inserted directly into the joint either just medial or lateral to the patella, depending on which side the joint line is more easily felt. In practice it is usually easier to identify the joint line on the lateral border of the patella. The space can be further widened by pressing on the opposite side of the patella

METHOD II

Position

The patient sits on a chair, with the foot flat on the ground and the knee flexed to a right angle.

aided by either traction, or by adducting the thumb, when the base of

› the abductor
e thumb nail.

Metacarpo-phalangeal joints and interphalangeal joints

These joints are injected from the dorsal aspect, the needle passing to one side of the mid line to avoid the extensor tendons.

It should be noted that when these joints are flexed, the joint line dorsally lies about ½ inch distal to the joint angle in the case of the metacarpo-phalangeal joints, and ¼ inch and ⅛ inch distal respectively for the proximal and distal interphalangeal joints.

Identification of the joint line is aided by traction on the finger.

Lower Limb

Hip joint (See Fig. 2.)

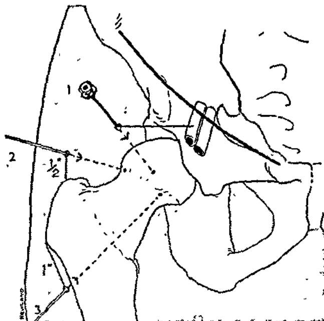


Fig. 2. Hip Joint.
1. Anterior approach. 2. Lateral approach 3 Caudo-lateral approach.

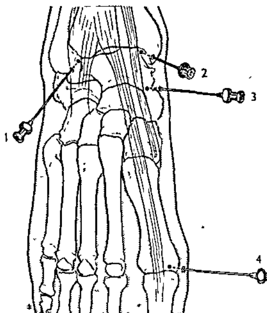
Caudo-lateral Approach

Position

The patient lies supine.

Method

The lower border of the greater trochanter is found, and the needle inserted about 1 inch below and 1 inch anterior to it.



[illegible]

Method

The anterior margin of the medial malleolus is found, and then the [illegible]

The joint may be injected in a similar manner through the angle made by the lateral malleolus and the lower anterior margin of the tibia, but this approach is more difficult

The Sub-taloid joints. (See Fig. 4.)

The sub-taloid joints are two in number.

The posterior, the talocalcanean joint, lies between the inferior surface of the talus and the posterior facet on the upper surface of the calcaneum.

The anterior, or talo-calcaneonavicular joint, is a ball and socket joint between the head of the talus and the cavity formed by the navicular, the spring ligament and the upper anterior surface of the calcaneum.

These two joints are separated by the interosseous ligament in the sinus tarsi and must be injected separately

It is at these two joints where the movements of inversion and eversion mainly occur.

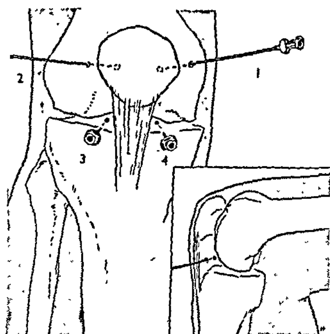


Fig 3 Knee Joint

1, 2 Approach to the joint, medial or lateral to patella, when the joint is extended
3, 4 Approach just above the lateral or medial condyle of the tibia, when the joint is flexed to a right angle.

Inset Medial side-view of knee joint to show the approach above the medial condyle.

Method

The ligamentum patellæ is first found in the mid line, and then the anterior margins of the lateral and medial condyle of the tibia are felt on either side of the tendon.

A depression is found over the joint, on each side of the ligamentum patellæ, bounded by the ligament in the mid line, the tibial condyle below, and the femoral condyle above

The needle is inserted directly into the joint just to one side of the ligamentum patellæ and just above the tibial condyle, the needle pointing slightly upwards and inwards.

It is usually easier to make the injection on the medial side of the patella

Ankle joint. (See Fig. 4)

Position

The patient lies on a couch with the leg extended, and the ankle joint plantar flexed.

Temporo-mandibular joint

Position

The patient lies on a couch with the head turned to the unaffected side.

Method

The joint lies just anterior to the tragus of the ear. The head of the mandible is felt moving forward when the mouth is opened, and the lower border of the zygomatic process is thus palpated immediately above and behind. The joint line is felt between these two bony points as a slight depression.

The injection is made with the jaw held widely open, the needle passing directly into this depression through the lateral aspect of the capsule, and about ½ inch anterior to the tragus to avoid the superficial temporal artery.

The author is indebted to Miss E Hewland for preparing the illustrations.

The Talo-calcaneonavicular joint

This joint is injected dorsally—the needle passing between the head of the talus and the navicular, just medial to the tendon of tibialis anterior. This approach is much easier than that from the medial side, when the needle passes into the joint just above the sustentaculum tali.

Position

The patient lies supine with the leg externally rotated, and the foot plantar flexed.

Method

The joint line between the head of the talus and the navicular is palpated over the dorsum of the foot, between the tendons of tibialis anterior and tibialis posterior, which is inserted into the tubercle of the navicular. The needle is inserted straight into the joint between these two tendons.

The Talocalcaneal joint and the interosseous ligament

This is injected through the sinus tarsi.

Position

The patient lies with the leg extended and *internally rotated*, and the foot plantar flexed and inverted.

Method

[illegible] te[illegible] e sir[illegible] wa[illegible] filtrated—and then on into the talocalcaneal joint.

Metatarso-phalangeal joints and interphalangeal joints. (See Fig. 4.)

[illegible] to one side of [illegible] ong traction on the toes, and the needle is inserted directly into the joint.

Coccydynia

Position

The patient is placed in the knee-elbow position.

Method

[illegible] ness found.

The needle is then inserted directly into the area of maximum tenderness.

It is of great assistance to inject procaine initially into the tender area to confirm that the needle is in the correct position.

To measure strength, pain and co-ordination.

4. Standing on toes, bare-footed, unaided.

0—30 seconds or more.
1—15 to 30 sec.
2—5 to 15 sec.
3—Less than 5 sec.
4—Not at all.

} If unsteady add 1 grade to each.

To measure pain and stiffness.

5. Jumping or hopping. Times in 10 sec.

0—Over 20 times.
1—15 to 20 times
2—5 to 15 times.
3—Less than 5 times.
4—Not at all.

} For pain or lack of balance add 1 grade.

For bed patients.

6. Leg bending and straightening—lying position—in 10 sec.

0—More than 10 times.
1—7 to 10 times.
2—3 to 7 times.
3—Less than 3 times.
4—Not at all.

} One extra grade is added if the range is not full.

Upper Limbs

To measure pain and stiffness.

7. Flailing arms in 10 sec. (backwards or forwards).

2 points for speed, i.e.:
0—Over 20 times.
1—10 to 20 times.
2—Less than 10 times.
2 points given for range, i e.:
0—Normal range
1—Moderate range.
2—Poor range.

To measure mobility and speed

8. Clothing. One point for each of the following:

(*a*) [illegible]
(*b*) [illegible]
(*c*) [illegible]
(*d*) [illegible]

APPENDIX II

ASSESSMENT OF CLINICAL PROGRESS

(a) FUNCTIONAL TESTS

Below are reproduced a selection of functional tests which we have found useful in following the progress of patients. It is simple to devise new and appropriate tests to suit individual cases. It is extremely difficult to evaluate *stiffness*,
vital importance to the pati
including several objective
carried out if possible at the same time of day to obviate the well-known diurnal variation in this symptom

Each test is marked in four different grades of disability, where 0=Normal and 4=Complete Incapacity. By selecting four or five

arthritis over the course of the years, and a strong case could be made for a standardized procedure of this sort in evaluating future therapeutic claims.

Lower Limbs

To measure strength, co-ordination and mobility.

1. Climbing on to a standard wooden chair, standing erect and then stepping off.

   0—Normal.
   1—Able to do it with difficulty or holding back of chair.
   2—Unable to do it at all.
   } For each leg. (i.e., total 4 points.)

2. "*Rheumatoid Flop*" (*i.e., terminal flop on sitting in a low* arm-chair without using hands.)

   Nil, slight, moderate, pronounced or very pronounced. Graded 0–4 points.

3. Kneeling on floor.

   0—Normal.
   1—With difficulty, but without using arms.
   2—Yes, but using arms.
   3—Almost.
   4—Not at all.

To measure strength, pain and co-ordination.

4 Standing on toes, bare-footed, unaided.

0—30 seconds or more. 1—15 to 30 sec. 2—5 to 15 sec. 3—Less than 5 sec. 4—Not at all.	If unsteady add 1 grade to each

To measure pain and stiffness.

5. Jumping or hopping. Times in 10 sec.

0—Over 20 times. 1—15 to 20 times. 2—5 to 15 times. 3—Less than 5 times. 4—Not at all.	For pain or lack of balance add 1 grade.

For bed patients

6. Leg bending and straightening—lying position—in 10 sec.

0—More than 10 times. 1—7 to 10 times. 2—3 to 7 times 3—Less than 3 times. 4—Not at all.	One extra grade is added if the range is not full.

Upper Limbs

To measure pain and stiffness.

7. Flailing arms in 10 sec. (backwards or forwards).

2 points for speed, i.e.:
0—Over 20 times.
1—10 to 20 times.
2—Less than 10 times
2 points given for range, i.e.:
0—Normal range.
1—Moderate range
2—Poor range.

To measure mobility and speed.

8 Clothing. One point for each of the following:

(*a*) Inability to tie a necktie.
(*b*) Inability to tie shoelaces.
(*c*) Inability to comb hair on back of head.
(*d*) Inability to put on a standard coat and button all the buttons.

To measure co-ordination, deformity and stiffness.

(For women.)

9 (*a*). Knitting.
Count the number of plain stitches knitted in 15 seconds. N.B. Most people know [illegible]

[illegible]

3—Less than half speed.
4—Not at all.

(For men)

9 (*b*). Writing a standard sentence.

2 points for speed, i.e.:
0—Normal.
1—Slightly slow.
2—Grossly slow and laboured.
2 points for dexterity, i.e.:
1—Slight unsteadiness.
2—Gross unsteadiness.

4—Unable to write at all.

To measure strength and pain.

10 Grip test (cuff blown up to 30 mm. Hg.).

0—260 mm. or over.
1—180-260 mm.
2—120-180 mm.
3—60-120 mm.
4—Below 60 mm.

Each hand assessed separately and results averaged.

In addition to these, we always carry out a *Walking test* as follows: The patient is instructed to walk—or shuffle—as far as he can in ten seconds as timed by a stop watch.
[illegible]

APPENDIX II

ASSESSMENT OF CLINICAL PROGRESS

(*b*) "Activities of Daily Living"

Since the ultimate objective in all treatment of arthritics is to rehabilitate them as far as possible to a normal social—and occupational—existence, it is desirable to try to evaluate the patient's disabilities in this context before and after treatment.

It is evident that factors other than the direct action of the drug on the disease may influence such activities, and that therefore the results

ments If the questions do not appear relevant to any particular case a further selection can be made from such a publication as *The Physical Demands of Daily Life* by Deaver and Brown (1945).

1. Ability to dress and undress.
   - 0—Yes, completely
   - 1—Yes, except for one or two garments
   - 2—About half
   - 3—Able to do a little
   - 4—Not at all

2. Speed of dressing and toilet activities.
   - 0—Normal.
   - 1—Slightly slow
   - 2—About half of normal speed.
   - 3—Less than half speed
   - 4—Not at all

3. Walking.
   - 0—Unlimited.
   - 1—Unlimited in distance, but some disability or tiredness
   - 2—Up to half a mile on the level.
   - 3—Up to 100 yards only.
   - 4—Not at all.

4. Household duties or own job.
   - 0—Normal.
   - 1—Normal, but with pain or difficulty
   - 2—Can only do part of duties, e.g., cannot kneel.
   - 3—Has to take days off completely (more than three in past month).
   - 4—Not able to do anything.

5. Eating activities.
   - 0—Normal.
   - 1—Unable to cut meat or spread butter.
   - 2—Unable to manipulate glass or cup.
   - 3—Unable to get food to mouth without gadgets
   - 4—Has to be fed completely.

6. Ability to shave or do hair.
   - 0—Normal.
   - 1—Slight difficulty.
   - 2—Moderate difficulty.
   - 3—Only able to do it occasionally.
   - 4—Not at all.

7. Transport.
   - 0—Normal
   - One point for each of the [illegible]
   - ([illegible]
   - ([illegible]
   - ([illegible]
   - 4 [illegible]

8. Getting in and out of a bath.
   - 0—Normal.
   - 1—Occasional difficulty.
   - 2—Able to get in and out and sit down, but not wash
   - 3—Able to get in, but not sit down or get out.
   - 4—Unable to get in or out.

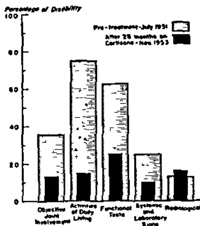
9. Ability to climb stairs
   - 0—Normal
   - 1—Slightly limited, or using handrail.
   - 2—Up normally, down one at a time.
   - 3—Up and down one step at a time, or backwards.
   - 4—Not at all.

10. Number of analgesic tablets* per 24 hours required to produce optimum functional status

    0—Up to 2 daily.
    1—Less than 4 daily.
    2—Less than 6 daily.
    3—Less than 8 daily.
    4—8 or more daily.

Whilst not a "functional test" in the strict sense of the word, this question is included here for convenience. With a co-operative patient allowed to take analgesic drugs at his own discretion it provides a valuable overall measurement of the progress of the disease.

Having carried out these assessments the results can be expressed in the form of a simple "balance sheet" of which this is an example:



This type of presentation is laborious and is only suggested for assessing the results of long term therapeutic trials

*The nature of the analgesic is unimportant provided that the same one is taken throughout the trial

APPENDIX II

ASSESSMENT OF CLINICAL PROGRESS

(c) SHORT-TERM TRIALS

The following type of chart is suggested for routine assessment of *short-term* trials.

Name: Mr. A. B. *Age:* 31. *Trial* Cortisone

Day	0	30	60	90
Date	10/4/55	10/5/55	9/6/55	9/7/55
Drug: Cortisone, mg.	0 .. 100 ..	75	50	75 ......
E.S.R.	105	38	36	20
Hb	9·3	9·6	11·1	12·6
R B C.	4·4	4·2	4·3	4·3
Weight	7·13	8·9	8·6	8·9
B.P.	*120/80*	*130/80*	*125/80*	*120/80*
Glycosuria	Nil	Trace	Nil	Nil
Other Data				
Subjective assessment*	100%	85%	80%	50%
Spontaneous Pain				
1 3rd Rt Prox. I P.	3	1	1	1
2. R. wrist	3	1	2	1
3 L knee	3	2	2	2
4. R ankle	3	1	2	1
Tenderness:				
1 3rd Lt. Prox I.P	3	2	2	2
2 L wrist	2	1	2	1
3 L knee	3	2	2	1
4 L Ankle	3	1	1	1
5 Jaw	3	1	0	0
6. Right Mid Tarsal	3	1	1	0
Range of Movement.				
1. Lt elbow supination	¼	½	½	Full
2 Rt knee Heel-buttock	11 in	8 in	8 in	7½ in.
3. Rt Shoulder Internal rotation	¼	½	½	¾
4. Jaw—bite	1·1 cm	1·6 cm	2 cm.	2 cm
Grip Test Rt hand	52	98	152	180
Lt hand	49	80	115	130
Ring Size Rt 3rd	26	22	23	23
Lt 2nd	28	25	25	25
Other Functional Tests: (measured as grade of disability)				
Leg bending	4	2	1	0
Flailing arms	4	2	2	0
Standing from a low chair	4	3	1	1
Analgesics per day	3	2	2	1

* 100 per cent represents arbitrarily subjective assessment of degree of disability on day of commencing treatment.

APPENDIX III

FURTHER READING

It is obviously impossible in a book such as this to give more than a few selected references from the vast literature on the steroid drugs The object of the following bibliography is to provide chiefly review articles, in the hope that the reader, by starting with one of these, may trace specific articles dealing with aspects of the theory and practical applications of steroid hormones which particularly interest him.

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